Inventor search history

```
=> d his L42

     (FILE 'HCAPLUS' ENTERED AT 16:41:51 ON 19 OCT 2009)
L42          16 S L41 AND (GUAN? OR BIOFILM? OR BIO(W)FILM? OR "BIOFILM" OR "CG

=> d que L42
L41          36 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  ("KARAOLIS D"/AU OR
                "KARAOLIS D K R"/AU OR "KARAOLIS DAVID"/AU OR "KARAOLIS DAVID
                K R"/AU)
L42          16 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L41 AND (GUAN? OR
                BIOFILM? OR BIO(W)FILM? OR "BIOFILM" OR "CGMP" OR "GMP")


=> d his L44

     (FILE 'MEDLINE, BIOSIS, EMBASE, DRUGU' ENTERED AT 16:49:19 ON 19 OCT 2009)
L44          44 S L42

=> d que L44
L41          36 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  ("KARAOLIS D"/AU OR
                "KARAOLIS D K R"/AU OR "KARAOLIS DAVID"/AU OR "KARAOLIS DAVID
                K R"/AU)
L42          16 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L41 AND (GUAN? OR
                BIOFILM? OR BIO(W)FILM? OR "BIOFILM" OR "CGMP" OR "GMP")
L44          44 SEA L42


=> dup rem L42 L44
FILE 'HCAPLUS' ENTERED AT 17:02:30 ON 19 OCT 2009
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2009 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'MEDLINE' ENTERED AT 17:02:30 ON 19 OCT 2009

FILE 'BIOSIS' ENTERED AT 17:02:30 ON 19 OCT 2009
Copyright (c) 2009 The Thomson Corporation

FILE 'EMBASE' ENTERED AT 17:02:30 ON 19 OCT 2009
Copyright (c) 2009 Elsevier B.V. All rights reserved.

FILE 'DRUGU' ENTERED AT 17:02:30 ON 19 OCT 2009
COPYRIGHT (C) 2009 THOMSON REUTERS
PROCESSING COMPLETED FOR L42
PROCESSING COMPLETED FOR L44
L58          25 DUP REM L42 L44 (35 DUPLICATES REMOVED)
                ANSWERS '1-16' FROM FILE HCAPLUS
                ANSWERS '17-25' FROM FILE BIOSIS
```

Inventor search results

=> d L58 1-25 ibib ab

L58 ANSWER 1 OF 25 HCAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2009:869974 HCAPLUS Full-text
TITLE: c-di-**GMP** as a vaccine adjuvant enhances protection against systemic methicillin-resistant Staphylococcus aureus (MRSA) infection
AUTHOR(S): Hu, Dong-Liang; Narita, Kouji; Hyodo, Mamoru; Hayakawa, Yoshihiro; Nakane, Akio; **Karaolis, David K. R.**
CORPORATE SOURCE: Department of Microbiology and Immunology, Hirosaki University Graduate School of Medicine, Hirosaki, 036-8562, Japan
SOURCE: Vaccine (2009), 27(35), 4867-4873
CODEN: VACCDE; ISSN: 0264-410X
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cyclic diguanylate (c-di-**GMP**) is a novel immunomodulator and immune enhancer that triggers a protective host innate immune response. The protective effect of c-di-**GMP** as a vaccine adjuvant against Staphylococcus aureus infection was investigated by s.c. (s.c.) vaccination with two different S. aureus antigens, clumping factor A (ClfA) and a nontoxic mutant staphylococcal enterotoxin C (mSEC), then i.v. (i.v.) challenge with viable methicillin-resistant S. aureus (MRSA) in a systemic infection model. Mice immunized with c-di-**GMP** plus mSEC or c-di-**GMP** plus ClfA vaccines then challenged with MRSA produced strong antigen-specific antibody responses demonstrating immunogenicity of the vaccines. Bacterial counts in the spleen and liver of c-di-**GMP** plus mSEC and c-di-**GMP** plus ClfA-immunized mice were significantly lower than those of control mice ($P < 0.001$). Mice immunized with c-di-**GMP** plus mSEC or c-di-**GMP** plus ClfA showed significantly higher survival rates at day 7 (87.5%) than those of the non-immunized control mice (33.3%) ($P < 0.05$). Furthermore, immunization of mice with c-di-**GMP** plus mSEC or c-di-**GMP** plus ClfA induced not only very high titers of IgG1 (IgG1), but c-di- **GMP** plus mSEC also induced significantly higher levels of IgG2a, IgG2b and IgG3 compared to alum adjuvant ($P < 0.01$ and $P < 0.001$, resp.) and c-di-**GMP** plus ClfA induced significantly higher levels of IgG2a, IgG2b and IgG3 compared to alum adjuvant ($P < 0.001$). Our results show that c-di-**GMP** should be developed as an adjuvant and immunotherapeutic to provide protection against systemic infection caused by S. aureus (MRSA).

L58 ANSWER 2 OF 25 HCAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2008:965252 HCAPLUS Full-text
DOCUMENT NUMBER: 150:349833
TITLE: c-di-**GMP** is an effective immunomodulator and vaccine adjuvant against pneumococcal infection
AUTHOR(S): Ogunniyi, Abiodun D.; Paton, James C.; Kirby, Alun C.; McCullers, Jonathan A.; Cook, Jan; Hyodo, Mamoru; Hayakawa, Yoshihiro; **Karaolis, David K. R.**
CORPORATE SOURCE: School of Molecular and Biomedical Science, University of Adelaide, 5005, Australia
SOURCE: Vaccine (2008), 26(36), 4676-4685
CODEN: VACCDE; ISSN: 0264-410X
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cyclic diguanylate (c-di-**GMP**) is a unique bacterial intracellular signaling mol. capable of stimulating enhanced protective innate immunity against various bacterial infections. The effects of intranasal pretreatment with c-di-**GMP**, or i.p. coadministration of c-di-**GMP** with the pneumolysin toxoid (PdB) or pneumococcal surface protein A (PspA) before pneumococcal challenge, were investigated in mice. We found that c-di-**GMP** had no significant direct short-term effect on the growth rate of Streptococcus pneumoniae either in vitro or in vivo. However, intranasal pretreatment of mice with c-di- **GMP** resulted in a significant decrease in bacterial load in lungs and blood after serotypes 2 and 3 challenge, and a significant decrease in lung titers after serotype 4 challenge. Potential cellular mediators of these enhanced protective responses were identified in lungs and draining lymph nodes. I.p. coadministration of c-di-**GMP** with PdB or PspA before challenge resulted in significantly higher antigen-specific antibody titers and increased survival of mice, compared to that obtained with alum adjuvant. These findings demonstrate that local or systemic c-di-**GMP** administration stimulates innate and adaptive immunity against invasive pneumococcal disease. We propose that c-di-**GMP** can be used as an effective broad spectrum immunomodulator and vaccine adjuvant to prevent infectious diseases. OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD

(1 CITINGS)

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 3 OF 25 HCAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 3

ACCESSION NUMBER: 2007:1122256 HCAPLUS Full-text

DOCUMENT NUMBER: 147:514687

TITLE: Cyclic di-**GMP** stimulates protective innate immunity in bacterial pneumonia

AUTHOR(S): **Karaolis, David K. R.**; Newstead, Michael W.; Zeng, Xianying; Hyodo, Mamoru; Hayakawa, Yoshihiro; Bhan, Urvhashi; Liang, Hallie; Standiford, Theodore J.

CORPORATE SOURCE: Intragenics Research Institute, Havre de Grace, MD, 21078, USA

SOURCE: Infection and Immunity (2007), 75(10), 4942-4950
CODEN: INFIBR; ISSN: 0019-9567

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Innate immunity is the primary mechanism by which extracellular bacterial pathogens are effectively cleared from the lung. We have previously shown that cyclic di-**GMP** (c-di-**GMP** [c-diguanylate]) is a novel small mol. immunomodulator and immunostimulatory agent that triggers protective host innate immune responses. Using a murine model of bacterial pneumonia, we show that local intranasal (i.n.) or systemic s.c. administration of c-di-**GMP** prior to intratracheal (i.t.) challenge with Klebsiella pneumoniae stimulates protective immunity against infection. Specifically, i.n. or s.c. administration of c-di- **GMP** 48 and 24 h prior to i.t. K. pneumoniae challenge resulted in significantly increased survival. Pretreatment with c-di-**GMP** resulted in a 5-fold reduction in bacterial CFU in the lung ($P < 0.05$) and an impressive > 1000-fold decrease in CFU in the blood ($P < 0.01$). C-di-**GMP** administration stimulated a robust innate response to bacterial challenge, characterized by enhanced accumulation of neutrophils and αβ T cells, as well as activated NK and αβ T lymphocytes, which was associated with earlier and more vigorous expression of chemokines and type I cytokines. Moreover, lung macrophages recovered from Klebsiella-infected mice pretreated with c-di-**GMP** expressed greater quantities of inducible nitric oxide synthase and nitric oxide ex vivo than did macrophages isolated from infected mice pretreated with the control, c-**GMP**. These findings demonstrate that c-di- **GMP** delivered in either a compartmentalized or systemic fashion stimulates protective innate immunity in the lung and protects mice against bacterial invasion. We propose that the cyclic dinucleotide c-di- **GMP** may be used clin. as an effective immunomodulator, immune enhancer, and vaccine

adjuvant to protect against respiratory infection and pneumonia in humans and animals. OS.CITING REF COUNT: 9 THERE ARE 9 CAPLUS RECORDS THAT CITE THIS RECORD
(9 CITINGS)
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 4 OF 25 HCAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 4
ACCESSION NUMBER: 2007:124392 HCAPLUS Full-text
DOCUMENT NUMBER: 146:204267
TITLE: Bacterial c-di-**GMP** Is an Immunostimulatory Molecule
AUTHOR(S): **Karaolis, David K. R.**; Means, Terry K.; Yang, De; Takahashi, Munehisa; Yoshimura, Teizo; Muraille, Eric; Philpott, Dana; Schroeder, John T.; Hyodo, Mamoru; Hayakawa, Yoshihiro; Talbot, Brian G.; Brouillette, Eric; Malouin, Francois
CORPORATE SOURCE: Intragenics Research Institute, Havre de Grace, MD, 21078, USA
SOURCE: Journal of Immunology (2007), 178(4), 2171-2181
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cyclic diguanylate (c-di-**GMP**) is a bacterial intracellular signaling mol. The authors have shown that treatment with exogenous c-di- **GMP** inhibits Staphylococcus aureus infection in a mouse model. The authors now report that c-di-**GMP** is an immodulator and immunostimulatory mol. Intramammary treatment of mice with c-di- **GMP** 12 and 6 h before S. aureus challenge gave a protective effect and a 10,000-fold reduction in CFUs in tissues. I.m. vaccination of mice with c-di-**GMP** coinjected with S. aureus clumping factor A (ClfA) Ag produced serum with significantly higher anti-ClfA IgG Ab titers compared with ClfA alone. I.p. injection of mice with c-di-**GMP** activated monocyte and granulocyte recruitment. Human immature dendritic cells (DCs) cultured in the presence of c-di-**GMP** showed increased expression of costimulatory mols. CD80/CD86 and maturation marker CD83, increased MHC class II and cytokines and chemokines such as IL-12, IFN-γ, IL-8, MCP-1, IFN-γ-inducible protein 10, and RANTES, and altered expression of chemokine receptors including CCR1, CCR7, and CXCR4. C-di-**GMP**-matured DCs demonstrated enhanced T cell stimulatory activity. C-di-**GMP** activated p38 MAPK in human DCs and ERK phosphorylation in human macrophages. C-di-**GMP** is stable in human serum. The authors propose that cyclic dinucleotides like c-di-**GMP** can be used clin. in humans and animals as an immunomodulator, immune enhancer, immunotherapeutic, immunoprophylactic, or vaccine adjuvant.
OS.CITING REF COUNT: 12 THERE ARE 12 CAPLUS RECORDS THAT CITE THIS RECORD (12 CITINGS)
REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 5 OF 25 HCAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 2005:714247 HCAPLUS Full-text
DOCUMENT NUMBER: 143:205833
TITLE: 3',5'-Cyclic diguanylic acid reduces the virulence of **biofilm**-forming Staphylococcus aureus strains in a mouse model of mastitis infection
AUTHOR(S): Brouillette, Eric; Hyodo, Mamoru; Hayakawa, Yoshihiro; **Karaolis, David K. R.**; Malouin, Francois
CORPORATE SOURCE: Centre d'Etude et de Valorisation de la Diversite Microbienne (CEVDM), Departement de biologie, Faculte des sciences, Universite de Sherbrooke, Sherbrooke, QC, J1K 2R1, Can.

SOURCE: Antimicrobial Agents and Chemotherapy (2005), 49(8), 3109-3113
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The cyclic dinucleotide 3',5'-cyclic diguanylic acid (c-di-**GMP**) is a naturally occurring small mol. that regulates important signaling systems in bacteria. The authors have recently shown that c-di- **GMP** inhibits Staphylococcus aureus **biofilm** formation in vitro and its adherence to HeLa cells. The authors now report that c-di- **GMP** treatment has an antimicrobial and antipathogenic activity in vivo and reduces, in a dose-dependent manner, bacterial colonization by **biofilm**-forming S. aureus strains in a mouse model of mastitis infection. Intramammary injections of 5 and 50 nmol of c-di-**GMP** decreased colonization (bacterial CFU) per g of gland by 0.79 ($P > 0.05$) and 1.44 ($P < 0.01$) logs, resp., whereas 200-nmol doses allowed clearance of the bacteria below the detection limit with a reduction of more than 4 logs ($P < 0.001$) compared to the untreated control groups. These results indicate that cyclic dinucleotides potentially represent an attractive and novel drug platform which could be used alone or in combination with other agents or drugs in the prevention, treatment, or control of infection. OS.CITING REF COUNT: 24 THERE ARE 24 CAPLUS RECORDS THAT CITE THIS RECORD (24 CITINGS)
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 6 OF 25 HCAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 6
ACCESSION NUMBER: 2005:229578 HCAPLUS Full-text
DOCUMENT NUMBER: 142:426617
TITLE: c-di-**GMP** (3'-5'-cyclic diguanylic acid) inhibits Staphylococcus aureus cell-cell interactions and **biofilm** formation
AUTHOR(S): **Karaolis, David K. R.**; Rashid, Mohammed H.; Chythanya, Rajanna; Luo, Wensheng; Hyodo, Mamoru; Hayakawa, Yoshihiro
CORPORATE SOURCE: Department of Epidemiology and Preventive Medicine, University of Maryland School of Medicine, Baltimore, MD, 21201, USA
SOURCE: Antimicrobial Agents and Chemotherapy (2005), 49(3), 1029-1038
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Staphylococcus aureus is an important pathogen of humans and animals, and antibiotic resistance is a public health concern. **Biofilm** formation is essential in virulence and pathogenesis, and the ability to resist antibiotic treatment results in difficult-to-treat and persistent infections. As such, novel antimicrobial approaches are of great interest to the scientific, medical, and agriculture communities. We recently proposed that modulating levels of the cyclic dinucleotide signaling mol., c-di-**GMP** (cyclic diguanylate [3',5'-cyclic diguanylic acid], cGpGp), has utility in regulating phenotypes of prokaryotes. We report that extracellular c-di-**GMP** shows activity against human clin. and bovine intramammary mastitis isolates of S. aureus, including methicillin-resistant S. aureus (MRSA) isolates. We show that chemical synthesized c-di-**GMP** is soluble and stable in water and physiol. saline and stable following boiling and exposure to acid and alkali. Treatment of S. aureus with extracellular c-di-**GMP** inhibited cell-to-cell (intercellular) adhesive interactions in liquid medium and reduced (>50%) **biofilm** formation in human and bovine isolates compared to untreated controls. C-di-**GMP** inhibited the adherence of S. aureus to human epithelial HeLa cells. The cyclic nucleotide analogs **cGMP** and cAMP had a lesser inhibitory effect on **biofilms**, while

5'-**GMP** had no major effect. We propose that cyclic dinucleotides such as c-di-**GMP**, used either alone or in combination with other antimicrobial agents, represent a novel and attractive approach in the development of intervention strategies for the prevention of **biofilms** and the control and treatment of infection.
OS.CITING REF COUNT: 30 THERE ARE 30 CAPLUS RECORDS THAT CITE THIS RECORD (30 CITINGS)
REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 7 OF 25 HCAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 7
ACCESSION NUMBER: 2007:662269 HCAPLUS Full-text
DOCUMENT NUMBER: 148:496266
TITLE: Chemical behavior of bis(3'-5')diguanylic acid in aqueous solutions
AUTHOR(S): Hyodo, Mamoru; Sato, Yumi; Hayakawa, Yoshihiro; **Karaolis, David K. R.**
CORPORATE SOURCE: Graduate School of Information Science/Human Informatics, Nagoya University, Chikusa, Nagoya, 464-8601, Japan
SOURCE: Nucleic Acids Symposium Series (2005), (49), 117-118
CODEN: NASSCJ
URL: http://nass.oxfordjournals.org/content/vol49/issue1/index.dtl
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB A unique behavior of bis(3'-5')diguanylic acid (c-di-**GMP**) under some conditions is described. It exists as the monomer in aprotic organic solvents such as DMSO. By contrast, it smoothly aggregates in water and in low-concentration aqueous solns. of some salts, such as sodium chloride and ammonium acetate, to give a mixture of many aggregates. The resulting multiple aggregates converge to the single compound (provably the monomer) in a >154 mM (0.9%) sodium chloride aqueous solution, in a >100 mM ammonium acetate buffer, and in a >100 mM phosphate buffer.
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 8 OF 25 HCAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 8
ACCESSION NUMBER: 2005:150086 HCAPLUS Full-text
DOCUMENT NUMBER: 142:329238
TITLE: 3',5'-Cyclic diguanylic acid (c-di-**GMP**) inhibits basal and growth factor-stimulated human colon cancer cell proliferation
AUTHOR(S): **Karaolis, David K. R.**; Cheng, Kunrong; Lipsky, Michael; Elnabawi, Ahmed; Catalano, Jennifer; Hyodo, Mamoru; Hayakawa, Yoshihiro; Raufman, Jean-Pierre
CORPORATE SOURCE: Department of Epidemiology and Preventive Medicine, University of Maryland School of Medicine, Baltimore, MD, 21201, USA
SOURCE: Biochemical and Biophysical Research Communications (2005), 329(1), 40-45
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The novel cyclic dinucleotide, 3',5'-cyclic diguanylic acid, cGpGp (c-di-**GMP**), is a naturally occurring small mol. that regulates important signaling mechanisms in prokaryotes. Recently, we showed that c-di- **GMP** has "drug-like"

properties and that c-di-**GMP** treatment might be a useful antimicrobial approach to attenuate the virulence and pathogenesis of Staphylococcus aureus and prevent or treat infection. In the present communication, we report that c-di-**GMP** (≥50 μM) has striking properties regarding inhibition of cancer cell proliferation in vitro. c-di-**GMP** inhibits both basal and growth factor (acetylcholine and epidermal growth factor)-induced cell proliferation of human colon cancer (H508) cells. Toxicity studies revealed that exposure of normal rat kidney cells and human neuroblastoma cells to c-di-**GMP** at biol. relevant doses showed no lethal cytotoxicity. Cyclic dinucleotides, such as c-di-**GMP**, represent an attractive and novel "drug-platform technol." that can be used not only to develop new antimicrobial agents, but also to develop novel therapeutic agents to prevent or treat cancer.
OS.CITING REF COUNT: 18 THERE ARE 18 CAPLUS RECORDS THAT CITE THIS RECORD (18 CITINGS)
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 9 OF 25 HCAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 9
ACCESSION NUMBER: 2004:50869 HCAPLUS Full-text
DOCUMENT NUMBER: 140:178223
TITLE: Role of exopolysaccharide, the rugose phenotype and VpsR in the pathogenesis of epidemic Vibrio cholerae
AUTHOR(S): Rashid, Mohammed H.; Rajanna, Chythanya; Zhang, Dalin; Pasquale, Vincenzo; Magder, Laurence S.; Ali, Afsar; Dumontet, Stefano; **Karaolis, David K. R.**
CORPORATE SOURCE: Department of Epidemiology and Preventive Medicine, University of Maryland School of Medicine, Baltimore, MD, 21201, USA
SOURCE: FEMS Microbiology Letters (2004), 230(1), 105-113
CODEN: FMLED7; ISSN: 0378-1097
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Vibrio cholerae, the causative agent of cholera, can produce an exopolysaccharide (EPS). Some strains can also phenotypically switch from a smooth to a 'rugose' phenotype characterized by small wrinkled colonies, overprodn. of EPS, increased **biofilm** formation in vitro and increased resistance to various stressful conditions. High frequency switching to the rugose phenotype is more common in epidemic strains than in non-pathogenic strains, suggesting EPS production and the rugose phenotype are important in cholera epidemiol. VpsR up-regulates Vibrio polysaccharide (VPS) genes and the synthesis of extracellular EPS (VPS). However, the function of VPS, the rugose phenotype and VpsR in pathogenesis is not well understood. The authors report that rugose strains of both classical and El Tor biotypes of epidemic V. cholerae are defective in the in vitro production of extracellular collagenase activity. In vivo studies in rabbit ileal loops suggest that VpsR mutants are attenuated in reactogenicity. Intestinal colonization studies in infant mice suggest that VPS production, the rugose phenotype and VpsR have a role in pathogenesis. The results indicate that regulated VPS production is important for promoting in vivo **biofilm** formation and pathogenesis. Addnl., VpsR might regulate genes with roles in virulence. Rugose strains appear to be a subpopulation of cells that might act as a 'helper' phenotype promoting the pathogenesis of certain strains. These studies provide new insight into the potential role of VPS, the rugose phenotype and VpsR in the pathogenesis of epidemic V. cholerae. OS.CITING REF COUNT: 8 THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (8 CITINGS)
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 10 OF 25 HCAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 10
ACCESSION NUMBER: 2003:688110 HCAPLUS Full-text

DOCUMENT NUMBER: 140:14616
TITLE: Analysis of the Vibrio pathogenicity island-encoded Mop protein suggests a pleiotropic role in the virulence of epidemic Vibrio cholerae
AUTHOR(S): Zhang, Dalin; Rajanna, Chythanya; Sun, Weiyun; **Karaolis, David K. R.**
CORPORATE SOURCE: Department of Epidemiology and Preventive Medicine, University of Maryland School of Medicine, Baltimore, MD, 21201, USA
SOURCE: FEMS Microbiology Letters (2003), 225(2), 311-318 CODEN: FMLED7; ISSN: 0378-1097
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Epidemic Vibrio cholerae contain a large essential virulence gene cluster called the Vibrio pathogenicity island (VPI). We recently reported that no in vitro difference in virulence was found in El Tor strain N16961 containing a mutation in the VPI-encoded mop gene but this mutant was hypervirulent and reactogenic in rabbit ileal loops. In this paper, we report in vitro studies showing that independent Mop mutants of strain 3083 are significantly attenuated (.apprx.40-fold) in cholera toxin (CT) production and have significantly increased motility and **biofilm** forming ability but appear to be unaffected in TcpA, hemagglutinin protease and hemolysin compared to their parent. The 3083 Mop mutant showed a 100-fold decrease in its in vivo intestinal colonization ability in the infant mouse competition assays. While reverse transcription polymerase chain reaction and phenotypic studies of a mop plasmid in both mutant and wild-type backgrounds suggest Mop is expressed by the plasmid, the differences in CT and **biofilm** formation could not be restored in any of the mutants. The inability to complement the Mop mutants in trans may be due either to the selection of secondary mutations or to mop possibly being part of an operon. Our findings that Mop is associated with CT, motility, **biofilm** formation and intestinal colonization support a hypothesis in which Mop has a pleiotropic role in the pathogenesis and persistence of epidemic V. cholerae. OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 11 OF 25 HCAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 11
ACCESSION NUMBER: 2003:808644 HCAPLUS Full-text
DOCUMENT NUMBER: 140:54341
TITLE: Identification of genes involved in the switch between the smooth and rugose phenotypes of Vibrio cholerae
AUTHOR(S): Rashid, Mohammed H.; Rajanna, Chythanya; Ali, Afsar; **Karaolis, David K. R.**
CORPORATE SOURCE: Department of Epidemiology and Preventive Medicine, University of Maryland School of Medicine, Baltimore, MD, 21201, USA
SOURCE: FEMS Microbiology Letters (2003), 227(1), 113-119 CODEN: FMLED7; ISSN: 0378-1097
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Vibrio cholerae can switch to a rugose' phenotype characterized by an exopolysaccharide (EPS) matrix, wrinkled colony morphol., increased **biofilm** formation and increased survival under specific conditions. The vps gene cluster responsible for the biosynthesis of the rugose EPS (rEPS) is pos. regulated by VpsR. We recently identified media (APW#3) promoting EPS production and the rugose phenotype and found epidemic strains switch at a higher frequency than non-pathogenic strains, suggesting this switch and the rugose phenotype are important

in cholera epidemiol. In this study, transposon mutagenesis on a smooth V. cholerae strain was used to identify mutants that were unable to shift to the rugose phenotype under inducing conditions to better understand the mol. basis of the switch. We identified vpsR, galE and vps previously associated with the rugose phenotype, and also identified genes not previously associated with the phenotype, including rfbD and rfbE having roles in LPS (lipopolysaccharide) synthesis and aroB and aroK with roles in aromatic amino acid synthesis. Addnl., a mutation in amiB encoding N-acetylmuramoyl-L-alanine amidase caused defects in the switch, motility and cell morphol. We also found that a gene encoding a novel regulatory protein we termed RocS (regulation of cell signaling) containing a GGDEF and EAL domains and associated with c-di-**GMP** levels is important for the rugose phenotype, EPS, **biofilm** formation and motility. We propose that modulation of cyclic dinucleotide (e.g. c-di-**GMP**) levels might have application in regulating various phenotypes of prokaryotes. Our study shows the mol. complexity of the switch between the smooth and rugose phenotypes of V. cholerae and may be relevant to similar phenotypes in other species. OS.CITING REF COUNT: 51 THERE ARE 51 CAPLUS RECORDS THAT CITE THIS
RECORD (52 CITINGS)
REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 12 OF 25 HCAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 12
ACCESSION NUMBER: 2002:862053 HCAPLUS Full-text
DOCUMENT NUMBER: 138:119678
TITLE: High-frequency rugose exopolysaccharide production by Vibrio cholerae
AUTHOR(S): Ali, Afsar; Rashid, Mohammed H.; **Karaolis, David K. R.**
CORPORATE SOURCE: Department of Epidemiology and Preventive Medicine, University of Maryland School of Medicine, Baltimore, MD, 21201, USA
SOURCE: Applied and Environmental Microbiology (2002), 68(11), 5773-5778
CODEN: AEMIDF; ISSN: 0099-2240
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB V. cholerae can shift to a "rugose" phenotype, thereby producing copious exopolysaccharide (EPS), which promotes its environmental survival and persistence. We report conditions that promote high-frequency rugose EPS production (HFRP), whereby cells switch at high frequency (≤80%) to rugose EPS production HFRP appeared to be more common in clin. strains, as HFRP was found in 6 of 19 clin. strains (32%) (including classical, El Tor, and non-O1 strains) but in only 1 of 16 environmental strains (6%). Differences were found between strains in rugose colony morphol., conditions promoting HFRP, the frequency of rugose-to-smooth (R-S) cell reversion, and **biofilm** formation. We propose that rugose EPS and HFRP provide an evolutionary and adaptive advantage to specific epidemic V. cholerae strains for increased persistence in the environment. OS.CITING REF COUNT: 25 THERE ARE 25 CAPLUS RECORDS THAT CITE THIS
RECORD (25 CITINGS)
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 13 OF 25 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:1396598 HCAPLUS Full-text
DOCUMENT NUMBER: 148:24432
TITLE: Method for stimulating the immune, inflammatory or neuroprotective response
INVENTOR(S): **Karaolis, David K. R.**
PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 60pp., Cont.-in-part of U.S. Ser. No. 79,886.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20070281897	A1	20071206	US 2007-669006	20070130
US 7592326	B2	20090922		
AU 2005221717	A1	20050922	AU 2005-221717	20050315
CA 2559802	A1	20050922	CA 2005-2559802	20050315
AU 2005222626	A1	20050929	AU 2005-222626	20050315
CA 2560058	A1	20050929	CA 2005-2560058	20050315
US 20060040887	A1	20060223	US 2005-79886	20050315
US 7569555	B2	20090804		
EP 1729781	A1	20061213	EP 2005-727318	20050315
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR				
EP 1740192	A2	20070110	EP 2005-753223	20050315
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR				
JP 2007529531	T	20071025	JP 2007-503996	20050315
JP 2007529532	T	20071025	JP 2007-503997	20050315

PRIORITY APPLN. INFO.:
US 2004-552721P P 20040315
US 2004-563692P P 20040420
US 2005-79886 A2 20050315
WO 2005-US8447 W 20050315
WO 2005-US8448 W 20050315

AB Cyclic di-**GMP**, or a cyclic dinucleotide analog thereof that has the same effect as cyclic di-**GMP**, stimulates or enhances immune or inflammatory response in a patient or enhances the immune response to a vaccine by serving as an adjuvant. Cyclic di-**GMP**, or a cyclic dinucleotide analog thereof, also has neuroprotective properties for use as a neuroprotective agent to inhibit, treat, or ameliorate the effects of injuries, diseases,.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L58 ANSWER 14 OF 25 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2006:351606 HCAPLUS Full-text
DOCUMENT NUMBER: 145:189078
TITLE: Organic synthesis, chemical properties, and biological activities of cyclic bis(3'-5)diguanylic acid (c-di-**GMP**) and its analogs
AUTHOR(S): Hyodo, Mamoru; Hayakawa, Yoshihiro; **Karaolis, David K. R.**
CORPORATE SOURCE: Graduate School of Human Informatics/Information Science, CREST/JST, Nagoya University, Chikusa, Nagoya, 464-8601, Japan
SOURCE: Yuki Gosei Kagaku Kyokaishi (2006), 64(4), 359-370
CODEN: YGKKAE; ISSN: 0037-9980
PUBLISHER: Yuki Gosei Kagaku Kyokai
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

AB A review. This paper describes efficient synthesis, chemical behaviors, and biol. activities of cyclic bis(3'-5')diguanylic acid (c-di-**GMP**) and its analogs, including cyclic bis(3'-5')**guanylic**-inosinic acid (c-GpIp), cyclic bis(3'-5')**guanylic**-adenylic acid (c-GpAp), and bis(3'-5')diguanylic acid

monophosphorothioate (c-GpGps). C-di- **GMP** was synthesized via two methods. Between the two methods, one method is more effective, particularly, for large-scale (gram-scale) synthesis to obtain the target compound in a high yield. While, c-GpIp, c-GpAp, and c-GpGps were synthesized via similar strategies. Studies on chemical behaviors of c-di-**GMP** indicated that these cyclic dinucleotides exist as the monomers in aprotic solvents such as DMSO. By contrast, it was shown that c-di-**GMP** smoothly aggregates to form a mixture of many compds. in water, in < 0.9% sodium chloride solns., in < 100 mM phosphate buffer solns., and in < 100 mM ammonium acetate buffer solns. All aggregated compds. smoothly revert to a single compound (probably an aggregate) by dissolving in a 0.9% sodium chloride solution (a physiol. salt solution), a > 100 mM phosphate buffer solution, or a > 100 mM ammonium acetate buffer solution Biol. investigation disclosed some novel activities of c-di-**GMP**, such as inhibition of **biofilm** formation of Staphylococcus aureus, inhibition of basal and growth factor stimulated human colon cancer cell proliferation, and reduction of the villus of **biofilm**-formed Staphylococcus aureus in a mouse model. OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD

(4 CITINGS)

L58 ANSWER 15 OF 25 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:300236 HCAPLUS Full-text
DOCUMENT NUMBER: 142:367640
TITLE: Method for attenuating virulence of microbial pathogens and inhibiting microbial **biofilm** formation by using c-di-**GMP** and cyclic dinucleotide analogs
INVENTOR(S): **Karaolis, David K. R.**
PATENT ASSIGNEE(S): University of Maryland, USA
SOURCE: PCT Int. Appl., 118 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005030186	A2	20050407	WO 2004-US23498	20040722
WO 2005030186	A3	20050714		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004275696	A1	20050407	AU 2004-275696	20040722
CA 2533873	A1	20050407	CA 2004-2533873	20040722
EP 1651242	A2	20060503	EP 2004-809506	20040722
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
JP 2007500697	T	20070118	JP 2006-521912	20040722
US 20070244059	A1	20071018	US 2006-**565591**	20061006
PRIORITY APPLN. INFO.:			US 2003-490029P P	20030728
			WO 2004-US23498 W	20040722

AB The present invention relates to the use of the cyclic dinucleotide c-di- **GMP**

and cyclic dinucleotide analogs thereof in a method for attenuating virulence of a microbial pathogen or for inhibiting or reducing colonization by a microbial pathogen. This method further inhibits microbial **biofilm** formation and is capable of treating bacterial infections. The microbial colonization or **biofilm** formation inhibited or reduced may be on the skin or on nasal or mucosal surface. The microbial colonization or **biofilm** formation inhibited can also be on the surfaces of medical devices, especially those in close contact with the patient, as well on the surfaces of industrial and construction material where microbial colonization and **biofilm** formation is of concern.
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L58 ANSWER 16 OF 25 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:1005971 HCAPLUS Full-text
DOCUMENT NUMBER: 143:279369
TITLE: Method using cyclic di-**GMP** or cyclic dinucleotide analog thereof for inhibiting cancer cell proliferation or increasing cancer cell apoptosis
INVENTOR(S): **Karaolis, David K.R.**; Raufman, Jean-Pierre
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 22 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20050203051	A1	20050915	US 2005-79779	20050315
AU 2005221717	A1	20050922	AU 2005-221717	20050315
CA 2559802	A1	20050922	CA 2005-2559802	20050315
WO 2005087238	A2	20050922	WO 2005-US8447	20050315
WO 2005087238	A3	20060309		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2005222626	A1	20050929	AU 2005-222626	20050315
CA 2560058	A1	20050929	CA 2005-2560058	20050315
WO 2005089777	A1	20050929	WO 2005-US8448	20050315
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1729781	A1	20061213	EP 2005-727318	20050315

R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR

EP 1740192 A2 20070110 EP 2005-753223 20050315

R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR

JP 2007529531 T 20071025 JP 2007-503996 20050315

JP 2007529532 T 20071025 JP 2007-503997 20050315

PRIORITY APPLN. INFO.: US 2004-552721P P 20040315

US 2004-563692P P 20040420

WO 2005-US8447 W 20050315

WO 2005-US8448 W 20050315

AB Cyclic di-**GMP** or cyclic dinucleotide analogs thereof can be used to inhibit cancer cell proliferation or to increase cancer cell apoptosis in vitro as well as in vivo in a patient. OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD

(2 CITINGS)

L58 ANSWER 17 OF 25 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN

ACCESSION NUMBER: 2009:518645 BIOSIS Full-text

DOCUMENT NUMBER: PREV200900519748

TITLE: Method for stimulating the immune, inflammatory or neuroprotective response.

AUTHOR(S): **Karaolis, David K. R.** [Inventor]; Anonymous

CORPORATE SOURCE: Baltimore, MD 21210 USA

PATENT INFORMATION: US 07569555 20090804

SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (AUG 4 2009)
CODEN: OGUPE7. ISSN: 0098-1133.

DOCUMENT TYPE: Patent

LANGUAGE: English

ENTRY DATE: Entered STN: 2 Sep 2009
Last Updated on STN: 2 Sep 2009

AB Cycic di-**GMP**, or a cyclic dinucleotide analogue thereof that has the same effect as cyclic di-**GMP**, stimulates or enhances immune or inflammatory response in a patient or enhances the immune response to a vaccine by serving as an adjuvant. Cyclic di-**GMP**, or a cyclic dinucleotide analogue thereof, also has neuroprotective properties for use as a neuroprotective agent to inhibit, treat, or ameliorate the effects of injuries, diseases, disorders or conditions that result in neurodegeneration.

L58 ANSWER 18 OF 25 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN

ACCESSION NUMBER: 2008:193052 BIOSIS Full-text

DOCUMENT NUMBER: PREV200800188893

TITLE: c-di-**GMP** stimulates protective innate immunity in bacterial pneumonia.

AUTHOR(S): **Karaolis, D. K. R.** [Reprint Author]; Newstead, M. W.; Zeng, X.; Liang, H.; Hyodo, M.; Hayakawa, Y.; Standiford, T. J.

CORPORATE SOURCE: Intragen Res Inst, Havre De Grace, MD USA

SOURCE: Abstracts of the General Meeting of the American Society for Microbiology, (2007) Vol. 107, pp. 266.
Meeting Info.: 107th General Meeting of the American-Society-for-Microbiology. Toronto, CANADA. 2007,.
Amer Soc Microbiol.
ISSN: 1060-2011.

DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)

LANGUAGE: English
ENTRY DATE: Entered STN: 19 Mar 2008
Last Updated on STN: 19 Mar 2008

L58 ANSWER 19 OF 25 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2008:237637 BIOSIS Full-text
DOCUMENT NUMBER: PREV200800233680
TITLE: c-di-**GMP** is an immunostimulatory molecule with prophylactic and adjuvant activity.
AUTHOR(S): **Karaolis, D. K. R.** [Reprint Author]; Means, T. K.; Brouillette, E.; Talbot, B. G.; Yang, D.; Muraille, E.; Hyodo, M.; Hayakawa, Y.; Malouin, F.
CORPORATE SOURCE: Univ Maryland, Baltimore, MD 21201 USA
SOURCE: Abstracts of the General Meeting of the American Society for Microbiology, (2006) Vol. 106, pp. 235.
Meeting Info.: 106th General Meeting of the American-Society-for-Microbiology. Orlando, FL, USA. May 21 -25, 2006. Amer Soc Microbiol.
ISSN: 1060-2011.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Apr 2008
Last Updated on STN: 2 Apr 2008

L58 ANSWER 20 OF 25 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:415877 BIOSIS Full-text
DOCUMENT NUMBER: PREV200510201468
TITLE: c-di-**GMP** as a novel anti-**biofilm** agent against Staphylococcus aureus.
AUTHOR(S): **Karaolis, D. K. R.** [Reprint Author]; Rashid, M. H.; Rajanna, C.; Buckles, E.; Luo, W.; Hyodo, M.; Hayakawa, Y.
SOURCE: Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy, (OCT-NOV 2004) Vol. 44, pp. 203.
Meeting Info.: 44th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC, USA. October 30 -November 02, 2004.
ISSN: 0733-6373.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 19 Oct 2005
Last Updated on STN: 19 Oct 2005

L58 ANSWER 21 OF 25 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2007:335423 BIOSIS Full-text
DOCUMENT NUMBER: PREV200700323424
TITLE: Regulation of Vibrio cholerae **biofilm** formation and intestinal colonization by Vibrio pathogenicity island recombinases.
AUTHOR(S): Rajanna, C. [Reprint Author]; Rashid, M. H.; **Karaolis, D. K. R.**
CORPORATE SOURCE: Univ Maryland, Sch Med, Baltimore, MD 21201 USA
SOURCE: Abstracts of the General Meeting of the American Society for Microbiology, (2004) Vol. 104, pp. 103.
Meeting Info.: 104th General Meeting of the

American-Society-for-Microbiology. New Orleans, LA, USA. May 23 -27, 2004. Amer Soc Microbiol.
ISSN: 1060-2011.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 30 May 2007
Last Updated on STN: 30 May 2007

L58 ANSWER 22 OF 25 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:544375 BIOSIS Full-text
DOCUMENT NUMBER: PREV200300546093
TITLE: The VPI-encoded int and VpiT of epidemic Vibrio cholerae have roles in high frequency rugose exopolysaccharide production (HFRP).
AUTHOR(S): Rajanna, C. [Reprint Author]; **Karaolis, D. K. R.** [Reprint Author]
CORPORATE SOURCE: University of Maryland, Baltimore, MD, USA
SOURCE: Abstracts of the General Meeting of the American Society for Microbiology, (2003) Vol. 103, pp. J-016. http://www.asmusa.org/mtgsrc/generalmeeting.htm. cd-rom.
Meeting Info.: 103rd American Society for Microbiology General Meeting. Washington, DC, USA. May 18-22, 2003. American Society for Microbiology.
ISSN: 1060-2011 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 19 Nov 2003
Last Updated on STN: 19 Nov 2003

AB Vibrio cholerae causes the epidemic diarrheal disease called cholera. V. cholerae can shift to a rugose colony phenotype in which the cells produce copious amounts of exopolysaccharide (EPS). The production of this EPS promotes the persistence of V. cholerae as it promotes **biofilm** formation and increased resistance to various stresses such as acid, chlorine, UV light, and complement. We have shown that some strains of V. cholerae can shift at high frequency to produce EPS in a process we call high frequency rugose EPS production (HFRP). HFRP was more common in clinical V. cholerae strains than in nonpathogenic strains suggesting that EPS production and HFRP is important in epidemic strains and might provide these strains with an adaptive advantage in certain niches. Epidemic strains of V. cholerae contain the Vibrio pathogenicity island (VPI) which is usually absent from nonpathogenic strains and which is essential for virulence. We show that the VPI-encoded integrase (int) and transposase-like (vpiT) genes affect EPS production and have roles in the switch to HFRP. A VpiT mutant in particular is significantly reduced in its ability to undergo HFRP and this defect can be complemented by a plasmid containing vpiT. Since genes on the VPI can affect HFRP, our results suggest that the VPI confers both virulence and increased environmental persistence in epidemic V. cholerae strains.

L58 ANSWER 23 OF 25 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:544373 BIOSIS Full-text
DOCUMENT NUMBER: PREV200300546092
TITLE: Genetic analysis of high frequency rugose exopolysaccharide production (HFRP) in epidemic Vibrio cholerae.
AUTHOR(S): Rashid, M. H. [Reprint Author]; Ali, A. [Reprint Author]; **Karaolis, D. K. R.** [Reprint Author]

CORPORATE SOURCE: University of Maryland School of Medicine, Baltimore, MD, USA
SOURCE: Abstracts of the General Meeting of the American Society for Microbiology, (2003) Vol. 103, pp. J-015. http://www.asmusa.org/mtgsrc/generalmeeting.htm. cd-rom. Meeting Info.: 103rd American Society for Microbiology General Meeting. Washington, DC, USA. May 18-22, 2003. American Society for Microbiology. ISSN: 1060-2011 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 19 Nov 2003
Last Updated on STN: 19 Nov 2003

AB Vibrio cholerae is the causative organism of the severe life threatening epidemic diarrheal disease called cholera. Some strains of V. cholerae can shift to a rugose colony phenotype whereby the cells produce copious amounts of exopolysaccharide (EPS). The production of this EPS promotes the persistence of V. cholerae as it promotes **biofilm** formation and increased resistance to various stresses such as acid, chlorine, UV light, and complement. Recently, we have shown that certain strains of V. cholerae can shift at high frequency to produce EPS in a process we called high frequency rugose EPS production (HFRP). We also found that HFRP was more common in epidemic V. cholerae strains than in non-pathogenic strains suggesting that EPS production and HFRP is important in epidemic strains and might provide these strains with an adaptive advantage in certain niches. In order to explore the genetic basis of HFRP in epidemic strains, we generated 10,000 mini-Tn5 mutants in the smooth 7th pandemic (El Tor) strain N16961 using minitransposon, pUT Km-2. The mutants were screened in order to identify mutants that were defective in their ability to switch to HFRP. A total of 29 mutants were found to be defective for HFRP. Sequencing and further analysis indicates that EPS biosynthetic genes and several regulatory genes have important roles in the genetic switch to HFRP. Our results suggest that HFRP is linked to a complex regulatory circuit in V. cholerae.

L58 ANSWER 24 OF 25 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:517549 BIOSIS Full-text
DOCUMENT NUMBER: PREV200300520027
TITLE: The Vibrio pathogenicity island-encoded Mop protein modulates cholera toxin production and **biofilm** formation in epidemic V. cholerae.
AUTHOR(S): Zhang, D. [Reprint Author]; Sun, W. [Reprint Author]; **Karaolis, D.** [Reprint Author]
CORPORATE SOURCE: University of Maryland School of Medicine, Baltimore, MD, USA
SOURCE: Abstracts of the General Meeting of the American Society for Microbiology, (2003) Vol. 103, pp. B-301. http://www.asmusa.org/mtgsrc/generalmeeting.htm. cd-rom. Meeting Info.: 103rd American Society for Microbiology General Meeting. Washington, DC, USA. May 18-22, 2003. American Society for Microbiology. ISSN: 1060-2011 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Nov 2003
Last Updated on STN: 5 Nov 2003

AB Epidemic cholera is a severe diarrheal disease caused by specific toxigenic strains of Vibrio cholerae. These strains possess an essential virulence cluster called the Vibrio pathogenicity island (VPI) that is typically absent from nonpathogenic strains. The VPI is 41.2-Kb in size and encodes 29 potential proteins, several of which have no known function. In order to better understand the pathogenesis of epidemic V. cholerae strains, we are characterizing the role of the VPI and its genes in virulence. We report that the VPI-encoded Mop protein is a predicted 34-kDa periplasmic protein which has no homolog in the database and contains a zinc metalloprotease motif. We constructed a mop mutation in V. cholerae 7th pandemic (El Tor) strain 3083 and found that Mop has no role in the expression of TcpA and hemaglutinin protease (HAP) or in motility, however, a Mop mutant is significantly attenuated in cholera toxin expression and increased in **biofilm** formation. Mop appears to be a protease that modulates the expression of several secreted proteins in V. cholerae. Our studies also suggest that there are differences between V. cholerae strains in the phenotypes that are modulated by Mop. Our in vitro studies support our previous in vivo results which showed that Mop is involved in the virulence of epidemic V. cholerae strains.

L58 ANSWER 25 OF 25 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN

ACCESSION NUMBER: 2002:597257 BIOSIS Full-text
DOCUMENT NUMBER: PREV200200597257
TITLE: Analysis of the genetic switch for phenotypic conversion between the smooth and rugose exopolysaccharide phenotypes of Vibrio cholerae.
AUTHOR(S): Rashid, M. H. [Reprint author]; Ali, A. [Reprint author]; **Karaolis, D. K. R.** [Reprint author]
CORPORATE SOURCE: University of Maryland School of Medicine, Baltimore, MD, USA
SOURCE: Abstracts of the General Meeting of the American Society for Microbiology, (2002) Vol. 102, pp. 263. print. Meeting Info.: 102nd General Meeting of the American Society for Microbiology. Salt Lake City, UT, USA. May 19-23, 2002. American Society for Microbiology. ISSN: 1060-2011.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 20 Nov 2002
Last Updated on STN: 20 Nov 2002

AB Cholera is a life threatening diarrheal disease caused by the bacterium Vibrio cholerae. Although the ability of epidemic V. cholerae strains to persist in the environment is critical in the epidemiology of cholera, the mechanisms underlying the endemicity and long-term persistence of epidemic V. cholerae strains are not well understood. Exopolysaccharide (EPS) production is important in **biofilm** formation and the persistence of many bacterial species. V. cholerae strains can under some conditions express a "rugose" colony phenotype due to copious production of EPS and which is thought to be important in the long-term persistence of the organism. We have recently discovered a phenomenon called "high frequency rugose EPS production" (HFRP) is unigue to epidemic V. cholerae strains in which a high frequency of smooth cells convert to rugose cells expressing copious EPS. We also found HFRP strains with a high rate of switching from the rugose to smooth phenotype. These findings suggest that EPS and HFRP are important in epidemic V. cholerae strains, however, the genetics and physiology of rugose EPS production are not well understood. Transposon mutagenesis and further genetic analysis was used to identify the genes involved in the genetic switch controlling the phenotypic shift between smooth and rugose phenotypes. Several mutants that

are defective in this phenotypic conversion have been identified. Since EPS is important for long-term persistence and since HFRP is unique to epidemic V. cholerae strains, our findings provide valuable information regarding the genetic switch of a phenomenon that appears to be important in the epidemiology of epidemic V. choleare strains.

Text search history

```
=> d his L31

     (FILE 'HCAPLUS' ENTERED AT 16:14:27 ON 19 OCT 2009)
L31          16 S L26 OR L30

=> d que L31
L3            1 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  CYCLIC GMP/CN
L4           24 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  ?CYCL?/CNS (L)
                ?GUANOS?/CNS (L) ?MONOPHOSPHAT?/CNS
L5          457 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  ?CYCL?/CNS (L)
                ?DIGUAN?/CNS
L6            1 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  L5 AND ?ACID?/CNS
L7            2 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  "C-DI-GMP"/ONS
L12           7 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  "CYCLIC DIGUANYLATE"/
                ONS
L16           7 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  "GUANOSINE 3',5'-CYCL
                IC MONOPHOSPHATE"/ONS
L17           1 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  "3'-5'-CYCLIC
                DIGUANYLIC ACID"/ONS
L19           1 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  "CYCLIC DIGUANYLIC
                ACID"/ONS
L21       40435 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  (L3 OR L4 OR L5 OR L6
                OR L7) OR L12 OR L16 OR L17 OR L19
L22       28335 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  ("CYCLIC GMP" OR
                CYCLIC(W)GMP OR (CYCLIC(3W)DIGUANYL?) OR "C-GMP" OR "CGMP" OR
                "C-DI-GMP" OR "BIS-(3',5') CYCLIC DIGUANYLIC ACID" OR "3',5'-CY
                CLIC DI-GMP" OR "CYCLIC DINUCLEOTIDE DI-GMP" OR  "BIS-(3'-5')-C
                YCLIC DIMERIC GUANOSINE MONOPHOSPHATE" OR  "C-(GPGP)" OR
                "CGPGP")
L23         847 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  ( "GUANOSINE 3',5'-CYC
                LIC MONOPHOSPHATE" OR  "3'-5'-CYCLIC DIGUANYLIC ACID" OR
                "BIS-(3'-5') CYCLIC DIGUANYLIC ACID" OR  "CYCLIC DIGUANYLIC
                ACID" OR  "CYCLIC-BIS(3',5')DIGUANYLIC ACID")
L24        1837 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  (L21 OR L22 OR L23)
                AND ((INHIBIT? OR REDUC? OR CONTROL? OR DIMINI? OR MINIM? OR
                DELAY? OR RETARD? OR PREVENT? OR PROPHYL? OR ELIMIN? OR
                DECREAS?)(5A)(MICROB? OR BACT? OR FUNG? OR PATHOGEN? OR
                BIOFILM? OR BIO(W)FILM? OR BIOSLIM? OR BIO(W)SLIM? OR COLONI?
                OR COLONY OR INFECT?))
L25         229 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L24 AND (SKIN? OR
                DERM? OR EPIDERM? OR NASAL? OR NASO? OR PHARYN? OR SINUS? OR
                SINO? OR MUCUS? OR MUCOS? OR MUCOUS? OR MEMBRAN?)
L26          10 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L25 AND ((MEDIC? OR
                SURGIC? OR THERAP? OR PATIENT? OR TREAT? OR RECONSTRUCT? OR
                ARTIFIC? OR REPLAC?)(5A)(DEVIC? OR IMPLEMENT? OR STENT? OR
                CATHET? OR IMPLANT? OR PROSTHET? OR INDWELL? OR IN(W)DWELL?))
L27          71 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L24 AND (BIOFILM? OR
                BIO(W)FILM? OR "IN VIVO" OR IN(W)VIVO? OR "IN VITRO" OR
                IN(W)VITR?)
L28          55 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L27 AND ((BIOFILM? OR
                BIO(W)FILM? OR BACT? OR PATHOGEN?) (3A) (INHIBIT? OR REDUC? OR
                CONTROL? OR DIMINI? OR MINIM? OR MITIGAT? OR PREVENT? OR
                STERIL? OR SANIT?))
L29          55 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L28 AND (BIOFILM? OR
                BIO(W)FILM?)
L30           7 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L29 AND ((ADMINIST?
                OR TREAT? OR APPLY? OR APPLICAT?) AND (PATIENT? OR MAMMAL? OR
```

```
                SUBJECT? OR CLINIC?))
L31           16 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L26 OR L30


=> d his L40

     (FILE 'HCAPLUS' ENTERED AT 16:41:51 ON 19 OCT 2009)
L40            3 S L39 AND ((ADMINIST? OR TREAT? OR APPLY? OR APPLICAT?) AND (PA

=> d que L40
L3             1 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  CYCLIC GMP/CN
L4            24 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  ?CYCL?/CNS (L)
                ?GUANOS?/CNS (L) ?MONOPHOSPHAT?/CNS
L5           457 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  ?CYCL?/CNS (L)
                ?DIGUAN?/CNS
L6             1 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  L5 AND ?ACID?/CNS
L7             2 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  "C-DI-GMP"/ONS
L12            7 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  "CYCLIC DIGUANYLATE"/
                ONS
L16            7 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  "GUANOSINE 3',5'-CYCL
                IC MONOPHOSPHATE"/ONS
L17            1 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  "3'-5'-CYCLIC
                DIGUANYLIC ACID"/ONS
L19            1 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  "CYCLIC DIGUANYLIC
                ACID"/ONS
L21        40435 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  (L3 OR L4 OR L5 OR L6
                OR L7) OR L12 OR L16 OR L17 OR L19
L34           47 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  (1044660-34-5/BI OR
                111-30-8/BI OR 132182-18-4/BI OR 132182-19-5/BI OR 132182-21-9/
                BI OR 132209-26-8/BI OR 132294-58-7/BI OR 146316-82-7/BI OR
                20816-12-0/BI OR 232933-52-7/BI OR 31348-80-8/BI OR 3353-33-1/B
                I OR 541-09-3/BI OR 548-62-9/BI OR 6018-53-7/BI OR 60307-63-3/B
                I OR 61093-23-0/BI OR 66-79-5/BI OR 75-56-9/BI OR 7681-52-9/BI
                OR 7722-84-1/BI OR 7782-50-5/BI OR 849214-01-3/BI OR 849214-02-
                4/BI OR 849214-03-5/BI OR 849214-04-6/BI OR 849214-05-7/BI OR
                849214-06-8/BI OR 849214-07-9/BI OR 849214-08-0/BI OR 849214-09
                -1/BI OR 849214-10-4/BI OR 849214-11-5/BI OR 849214-12-6/BI OR
                849214-13-7/BI OR 849214-14-8/BI OR 849214-15-9/BI OR 849214-16
                -0/BI OR 849447-99-0/BI OR 849448-00-6/BI OR 849448-01-7/BI OR
                849448-02-8/BI OR 849448-03-9/BI OR 9004-34-6/BI OR 9012-56-0/B
                I OR 9013-25-6/BI OR 9042-14-2/BI)
L35            2 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  L34 AND L21
L36            1 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  61093-23-0/RN
L37            3 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  61093-23-0/CRN
L38           55 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  (L35 OR L36 OR L37)
                AND ((INHIBIT? OR REDUC? OR CONTROL? OR DIMINI? OR MINIM? OR
                DELAY? OR RETARD? OR PREVENT? OR PROPHYL? OR ELIMIN? OR
                DECREAS?)(5A)(MICROB? OR BACT? OR FUNG? OR PATHOGEN? OR
                BIOFILM? OR BIO(W)FILM? OR BIOSLIM? OR BIO(W)SLIM? OR COLONI?
                OR COLONY OR INFECT?))
L39           36 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L38 AND (BIOFILM? OR
                BIO(W)FILM? OR "BIOFILM")
L40            3 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L39 AND ((ADMINIST?
                OR TREAT? OR APPLY? OR APPLICAT?) AND (PATIENT? OR MAMMAL? OR
                SUBJECT? OR CLINIC?))


=> d his L57

     (FILE 'MEDLINE, BIOSIS, EMBASE, DRUGU' ENTERED AT 16:49:19 ON 19 OCT 2009)
```

```
L57          24 S L54 OR L56

=> d que L57
L3            1 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  CYCLIC GMP/CN
L5          457 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  ?CYCL?/CNS (L)
                ?DIGUAN?/CNS
L6            1 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  L5 AND ?ACID?/CNS
L7            2 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  "C-DI-GMP"/ONS
L12           7 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  "CYCLIC DIGUANYLATE"/
                ONS
L16           7 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  "GUANOSINE 3',5'-CYCL
                IC MONOPHOSPHATE"/ONS
L17           1 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  "3'-5'-CYCLIC
                DIGUANYLIC ACID"/ONS
L19           1 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  "CYCLIC DIGUANYLIC
                ACID"/ONS
L22       28335 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  ("CYCLIC GMP" OR
                CYCLIC(W)GMP OR (CYCLIC(3W)DIGUANYL?) OR "C-GMP" OR "CGMP" OR
                "C-DI-GMP" OR "BIS-(3',5') CYCLIC DIGUANYLIC ACID" OR "3',5'-CY
                CLIC DI-GMP" OR "CYCLIC DINUCLEOTIDE DI-GMP" OR  "BIS-(3'-5')-C
                YCLIC DIMERIC GUANOSINE MONOPHOSPHATE" OR  "C-(GPGP)" OR
                "CGPGP")
L23         847 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  ( "GUANOSINE 3',5'-CYC
                LIC MONOPHOSPHATE" OR  "3'-5'-CYCLIC DIGUANYLIC ACID" OR
                "BIS-(3'-5') CYCLIC DIGUANYLIC ACID" OR  "CYCLIC DIGUANYLIC
                ACID" OR  "CYCLIC-BIS(3',5')DIGUANYLIC ACID")
L45       58517 SEA L3 OR L6 OR L7 OR L12 OR L16 OR L17 OR L19
L46       58359 SEA L45 AND (L22 OR L23)
L47         118 SEA L46 AND (BIOFILM? OR BIO(W) FILM? OR "BIOFILM")
L49           6 SEA L47 AND ((ADMINIST? OR TREAT? OR APPLY? OR APPLICAT?) AND
                (PATIENT? OR MAMMAL? OR SUBJECT? OR CLINIC?))
L50          44 SEA L47 AND ((INHIBIT? OR REDUC? OR CONTROL? OR DIMINI? OR
                MINIM? OR DELAY? OR RETARD? OR PREVENT? OR PROPHYL? OR ELIMIN?
                OR DECREAS?)(5N)(MICROB? OR BACT? OR FUNG? OR PATHOGEN? OR
                BIOFILM? OR BIO(W) FILM? OR BIOSLIM? OR BIO(W) SLIM? OR
                COLONI? OR COLONY OR INFECT?))
L51          15 SEA L47 AND (SKIN? OR DERM? OR EPIDERM? OR NASAL? OR NASO? OR
                PHARYN? OR SINUS? OR SINO? OR MUCUS? OR MUCOS? OR MUCOUS? OR
                MEMBRAN?)
L52           9 SEA L50 AND (L49 OR L51)
L53          10 SEA L50 AND (ADMINIST? OR PATIENT? OR MAMMAL? OR TREAT?)
L54          24 SEA L49 OR (L51 OR L52 OR L53)
L55          38 SEA L47 AND (STAPHYLOCOCC? OR VIBRIO? OR GONOCOCC?)
L56          10 SEA L54 AND L55
L57          24 SEA L54 OR L56


=> dup rem L31 L40 L57
PROCESSING COMPLETED FOR L31
PROCESSING COMPLETED FOR L40
PROCESSING COMPLETED FOR L57
L59          30 DUP REM L31 L40 L57 (13 DUPLICATES REMOVED)
                ANSWERS '1-16' FROM FILE HCAPLUS
                ANSWERS '17-28' FROM FILE MEDLINE
                ANSWERS '29-30' FROM FILE EMBASE
```

Text search results: HCAPLUS

=> d L59 1-16 ibib ed abs hitrn

L59 ANSWER 1 OF 30 HCAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 2005:300236 HCAPLUS Full-text
DOCUMENT NUMBER: 142:367640
TITLE: Method for attenuating virulence of **microbial pathogens** and **inhibiting microbial biofilm** formation by using **c-di-GMP** and cyclic dinucleotide analogs
INVENTOR(S): Karaolis, David K. R.
PATENT ASSIGNEE(S): University of Maryland, USA
SOURCE: PCT Int. Appl., 118 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005030186	A2	20050407	WO 2004-US23498	20040722
WO 2005030186	A3	20050714		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004275696	A1	20050407	AU 2004-275696	20040722
CA 2533873	A1	20050407	CA 2004-2533873	20040722
EP 1651242	A2	20060503	EP 2004-809506	20040722
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
JP 2007500697	T	20070118	JP 2006-521912	20040722
US 20070244059	A1	20071018	US 2006-**565591**	20061006
PRIORITY APPLN. INFO.:			US 2003-490029P P	20030728
			WO 2004-US23498 W	20040722

ED Entered STN: 07 Apr 2005
AB The present invention relates to the use of the cyclic dinucleotide **c-di-GMP** and cyclic dinucleotide analogs thereof in a method for attenuating virulence of a **microbial pathogen** or for **inhibiting** or **reducing colonization** by a **microbial pathogen**. This method further **inhibits microbial biofilm** formation and is capable of **treating** bacterial infections. The **microbial colonization** or **biofilm** formation **inhibited** or **reduced** may be on the **skin** or on **nasal** or **mucosal** surface. The **microbial colonization** or **biofilm** formation **inhibited** can also be on the surfaces of **medical devices**, especially those in close contact with the **patient**, as well on the surfaces of industrial and construction material where microbial colonization and **biofilm** formation is of concern.
IT **146316-82-7**
RL: PRPH (Prophetic)

(Method for attenuating virulence of **microbial pathogens** and **inhibiting microbial biofilm** formation by using **c-di-GMP** and cyclic dinucleotide analogs)

IT **61093-23-0D**, carboxy/phosphoalkylene ether derivs.
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuating virulence of **microbial pathogens** and **inhibiting microbial biofilm** formation by using **c-di-GMP** and cyclic dinucleotide analogs)

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L59 ANSWER 2 OF 30 HCAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 6
ACCESSION NUMBER: 2005:887352 HCAPLUS Full-text
DOCUMENT NUMBER: 143:402354
TITLE: Aminoglycoside antibiotics induce bacterial **biofilm** formation
AUTHOR(S): Hoffman, Lucas R.; D'Argenio, David A.; MacCoss, Michael J.; Zhang, Zhaoying; Jones, Roger A.; Miller, Samuel I.
CORPORATE SOURCE: Department of Pediatrics, University of Washington, Seattle, WA, 98195, USA
SOURCE: Nature (London, United Kingdom) (2005), 436(7054), 1171-1175
CODEN: NATUAS; ISSN: 0028-0836
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 25 Aug 2005
AB **Biofilms** are adherent aggregates of bacterial cells that form on biotic and abiotic surfaces, including human tissues. **Biofilms** resist antibiotic **treatment** and contribute to bacterial persistence in chronic infections. Hence, the elucidation of the mechanisms by which **biofilms** are formed may assist in the **treatment** of chronic infections, such as Pseudomonas aeruginosa in the airways of **patients** with cystic fibrosis. Here we show that subinhibitory concns. of aminoglycoside antibiotics induce **biofilm** formation in P. aeruginosa and Escherichia coli. In P. aeruginosa, a gene, which we designated aminoglycoside response regulator (arr), was essential for this induction and contributed to **biofilm**-specific aminoglycoside resistance. The arr gene is predicted to encode an inner-membrane phosphodiesterase whose substrate is cyclic di-guanosine monophosphate (**c-di-GMP**)-a bacterial second messenger that regulates cell surface adhesiveness. We found that membranes from arr mutants had diminished **c-di- GMP** phosphodiesterase activity, and P. aeruginosa cells with a mutation changing a predicted catalytic residue of Arr were defective in their **biofilm** response to tobramycin. Furthermore, tobramycin-inducible **biofilm** formation was **inhibited** by exogenous GTP, which is known to inhibit **c-di- GMP** phosphodiesterase activity. Our results demonstrate that **biofilm** formation can be a specific, defensive reaction to the presence of antibiotics, and indicate that the mol. basis of this response includes alterations in the level of **c-di-GMP** .

IT **57-92-1**, Streptomycin, biological studies **61093-23-0** **338732-46-0**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(aminoglycoside antibiotics induce bacterial **biofilm** formation)

OS.CITING REF COUNT: 95 THERE ARE 95 CAPLUS RECORDS THAT CITE THIS RECORD (95 CITINGS)
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L59 ANSWER 3 OF 30 HCAPLUS COPYRIGHT 2009 ACS on STN DUPLICATE 7
ACCESSION NUMBER: 2005:229578 HCAPLUS Full-text
DOCUMENT NUMBER: 142:426617
TITLE: **c-di-GMP (3'-5'-cyclic diguanylic acid)** inhibits Staphylococcus aureus cell-cell interactions and **biofilm** formation
AUTHOR(S): Karaolis, David K. R.; Rashid, Mohammed H.; Chythanya, Rajanna; Luo, Wensheng; Hyodo, Mamoru; Hayakawa, Yoshihiro
CORPORATE SOURCE: Department of Epidemiology and Preventive Medicine, University of Maryland School of Medicine, Baltimore, MD, 21201, USA
SOURCE: Antimicrobial Agents and Chemotherapy (2005), 49(3), 1029-1038
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 17 Mar 2005
AB Staphylococcus aureus is an important pathogen of humans and animals, and antibiotic resistance is a public health concern. **Biofilm** formation is essential in virulence and pathogenesis, and the ability to resist antibiotic **treatment** results in difficult-to- **treat** and persistent infections. As such, novel antimicrobial approaches are of great interest to the scientific, medical, and agriculture communities. We recently proposed that modulating levels of the cyclic dinucleotide signaling mol., **c-di- GMP (cyclic diguanylate [3', 5'-cyclic diguanylic acid], cGpGp)**, has utility in regulating phenotypes of prokaryotes. We report that extracellular **c-di-GMP** shows activity against human **clin.** and bovine intramammary mastitis isolates of S. aureus, including methicillin-resistant S. aureus (MRSA) isolates. We show that chemical synthesized **c-di- GMP** is soluble and stable in water and physiol. saline and stable following boiling and exposure to acid and alkali. **Treatment** of S. aureus with extracellular **c-di-GMP** inhibited cell-to-cell (intercellular) adhesive interactions in liquid medium and **reduced** (>50%) **biofilm** formation in human and bovine isolates compared to untreated controls. **C- di-GMP** inhibited the adherence of S. aureus to human epithelial HeLa cells. The cyclic nucleotide analogs **cGMP** and cAMP had a lesser **inhibitory** effect on **biofilms**, while 5'-GMP had no major effect. We propose that cyclic dinucleotides such as **c-di-GMP**, used either alone or in combination with other antimicrobial agents, represent a novel and attractive approach in the development of intervention strategies for the **prevention** of **biofilms** and the **control** and **treatment** of **infection**.
IT **61093-23-0**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**c-di-GMP (3'-5'-cyclic diguanylic acid)** inhibits Staphylococcus aureus cell-cell interactions and **biofilm** formation)
OS.CITING REF COUNT: 30 THERE ARE 30 CAPLUS RECORDS THAT CITE THIS RECORD (30 CITINGS)
REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L59 ANSWER 4 OF 30 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2009:1139004 HCAPLUS Full-text
DOCUMENT NUMBER: 151:373900
TITLE: Use of ellagitannins as **inhibitors** of **bacterial** quorum sensing

INVENTOR(S): Mathee, Kalai; Adonizio, Allison L.; Ausubel, Frederick; Clardy, Jon; Bennett, Bradley; Downum, Kelsey
PATENT ASSIGNEE(S): The Florida International Uinversity, USA
SOURCE: PCT Int. Appl., 59pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009114810	A2	20090917	WO 2009-US37163	20090313

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2008-36812P P 20080314
ED Entered STN: 18 Sep 2009
AB The invention provides materials and methods for the **inhibition** of **bacterial** quorum sensing (QS). The invention also provides methods for treating bacterial infections by administration of one or more ellagitannins in amount effective to **inhibit bacterial** QS.
IT **57-92-1**, Streptomycin **57-92-1D**, Streptomycin, derivs.
RL: PAC (Pharmacological activity); TEM (Technical or engineered material use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ellagitannins as **inhibitors** of **bacterial** quorum sensing, use in treatment of bacterial infection, and use with other agents)

L59 ANSWER 5 OF 30 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2009:1080981 HCAPLUS Full-text
DOCUMENT NUMBER: 151:329919
TITLE: Recombinant **bacteriophage** containing nucleotides for **inhibiting** antibiotic resistance, survival, SOS response and/or defense genes, and their use in combination of antimicrobial agents in **eliminating bacteria** in animals or surfaces
INVENTOR(S): Collins, James J.; Lu, Timothy Kuan-Ta
PATENT ASSIGNEE(S): Boston University, USA; Massachusetts Institute of Technology
SOURCE: PCT Int. Appl., 229pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2009108406	A2	20090903	WO 2009-US30755	20090112

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2008-20197P P 20080110

ED Entered STN: 04 Sep 2009

AB The invention provides recombinant, genetically engineered bacteriophages, and their use in combination with an antimicrobial agent to **reduce** or **eliminate** **bacteria** in animals (including humans), and/or on surfaces. Specifically, recombinant bacteriophages, developed from M13 or T7, contain nucleic acids designed to: (a) **inhibit** at least one **bacterial** antibiotic resistance gene (such as cat, vanA or mecD) and/or survival gene (such as RecA, RecB, RecC, spot or RelA); (b) repress at least one SOS response or defense gene; and/or (c) express a protein (such as porin) that increases susceptibility of a bacterial cell to an antimicrobial agent, wherein said protein modifies a specific pathway. The invention also provides compns. and kits comprising said recombinant bacteriophages and at least on antimicrobial agent.

IT **57-92-1D**, Streptomycin, variant and/or analog thereof
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bacteriophage** containing nucleotides for **inhibiting** antibiotic resistance, survival, SOS response and/or defense genes, and their use in combination of antimicrobial agents in **eliminating** **bacteria** in animals or surfaces)

L59 ANSWER 6 OF 30 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:416834 HCAPLUS Full-text
DOCUMENT NUMBER: 148:397490
TITLE: Analyte sensing device with external control unit and implantable biosensor for continuously monitoring metabolic levels of analytes
INVENTOR(S): Grantham, Daniel H.; Jain, Faquir; Papadimitrakopoulos, Fotios; Burgess, Diane
PATENT ASSIGNEE(S): University of Connecticut, USA; Optoelectronics Systems Consulting, Inc. "Osci"; Grantham, G., Deborah; Salisbury, Jane
SOURCE: PCT Int. Appl., 76pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

WO 2008039543	A1	20080403	WO 2007-US21042	20070927

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL,

PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW,
GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
BY, KG, KZ, MD, RU, TJ, TM

US 20080154101	A1	20080626	US 2007-862866	20070927
EP 2079358	A1	20090722	EP 2007-839072	20070927

R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
IS, IT, LI, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR

PRIORITY APPLN. INFO.: US 2006-827104P P 20060927
WO 2007-US21042 W 20070927

ED Entered STN: 03 Apr 2008

AB Disclosed herein is an analyte sensing device capable of continuously monitoring metabolic levels of a plurality of analytes. The device comprises an external unit, which, for example, could be worn around the wrist like a wristwatch or could be incorporated into a cell phone or PDA device, and an implantable sensor platform that is suitable, for example, for implantation under the **skin**. The external device and the internal device are in wireless communication. In one embodiment, the external device and the internal device are operationally linked by a feedback system. In one embodiment, the internal device is encapsulated in a biocompatible coating capable of controlling the local tissue environment in order to prevent/minimize inflammation and fibrosis, promote neo-angiogenesis and wound healing and this facilitate device functionality.

IT **57-92-1**, Streptomycin
RL: TEM (Technical or engineered material use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(analyte sensing device with external control unit and implantable biosensor for continuously monitoring metabolic levels of analytes)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L59 ANSWER 7 OF 30 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:160537 HCAPLUS Full-text
DOCUMENT NUMBER: 148:209646
TITLE: Plate for selection of antibiotics against **biofilm** infections
INVENTOR(S): Olson, Merle E.; Ceri, Howard
PATENT ASSIGNEE(S): MBEC Bioproducts Inc., Can.
SOURCE: PCT Int. Appl., 59pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008014581	A1	20080207	WO 2006-CA1226	20060724

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP,
KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN,
MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU,
SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG,
US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,

CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

CA 2616526	A1	20070122	CA 2006-2616526	20060724
US 20080318269	A1	20081225	US 2008-996480	20080819
PRIORITY APPLN. INFO.:			US 2005-701858P	P 20050722
			WO 2006-CA1226	W 20060724

ED Entered STN: 08 Feb 2008

AB This invention is a diagnostic plate that can be used to select antibiotic combinations with efficacy against microorganisms growing as a **biofilm**. The plate allows growth of **biofilm** on a plurality of projections, and the subsequent simultaneous challenge of **biofilms** on all projections of the plate to independent concns. and combinations of anti-**biofilm** agents. Resistance of microorganisms to antibiotics is higher when they grow as a **biofilm**, as compared to when they grow in a planktonic state which is usually used to determine their level of antibiotic sensitivity. Growth of microorganisms that slough off the **biofilm** in the anti- **biofilm** agent challenge dets. the Min. **Inhibitory** Concentration (MIC) which relates to sensitivity of the microorganisms in a planktonic state. Growth of any surviving microorganisms from the **biofilm** in a subsequent recovery step dets. the **Minimal Biofilm** Eradication Concentration (MBEC) which relates to the sensitivity of the microorganisms growing as a **biofilm**. Enumeration of the surviving microorganisms in the recovery step dets. the Min. Biocidal Concentration (MBC). A Staphylococcus test plate was developed to evaluate antibiotics and antibiotic combinations against Staphylococcus aureus **biofilms**. The 96-well plate had gentamicin, clindamycin, cefazolin, cloxacillin, rifampin, vancomycin, linezolid, ampicillin sublactam, ciprofloxacin, various combinations of the antibiotics, a growth control, and a sterility control. The sensitivity of planktonic and **biofilm** forms of S. aureus to individual and combination agents could be determined within about 48 h. S. aureus was sensitive to multiple antibiotics and antibiotic combinations as planktonic forms, but was significantly more resistant as a **biofilm**.

IT **57-92-1**

RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); PRPH (Prophetic); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(plate for selection of antibiotics and fungicides against **biofilm** infections)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L59 ANSWER 8 OF 30 HCAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2008:157144 HCAPLUS Full-text

DOCUMENT NUMBER: 148:209645

TITLE: Plate for selection of antibiotics against **biofilm** infections

INVENTOR(S): Olson, Merle E.; Ceri, Howard

PATENT ASSIGNEE(S): MBEC Bioproducts Inc., Can.

SOURCE: PCT Int. Appl., 64pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008014580	A1	20080207	WO 2006-CA1218	20060724

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,

GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP,
KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN,
MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU,
SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG,
US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,
CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM

CA 2616559	A1	20080124	CA 2006-2616559	20060724
EP 1915458	A1	20080430	EP 2006-761179	20060724
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, RS				
KR 2008081891	A	20080910	KR 2008-704354	20080222
CN 101283104	A	20081008	CN 2006-80030645	20080222
US 20080318268	A1	20081225	US 2008-996478	20080819
PRIORITY APPLN. INFO.:			US 2005-701858P P	20050722
			WO 2006-CA1218 W	20060724

ED Entered STN: 07 Feb 2008

AB This invention is a diagnostic plate that can be used to select antibiotic combinations with efficacy against microorganisms growing as a **biofilm**. The plate allows growth of **biofilm** on a plurality of projections, and the subsequent simultaneous challenge of **biofilms** on all projections of the plate to independent concns. and combinations of anti-**biofilm** agents. Resistance of microorganisms to antibiotics is higher when they grow as a **biofilm**, as compared to when they grow in a planktonic state which is usually used to determine their level of antibiotic sensitivity. Growth of microorganisms that slough off the **biofilm** in the anti- **biofilm** agent challenge dets. the Min. **Inhibitory** Concentration (MIC) which relates to sensitivity of the microorganisms in a planktonic state. Growth of any surviving microorganisms from the **biofilm** in a subsequent recovery step dets. the **Minimal Biofilm** Eradication Concentration (MBEC) which relates to the sensitivity of the microorganisms growing as a **biofilm**. Enumeration of the surviving microorganisms in the recovery step dets. the Min. Biocidal Concentration (MBC). A Staphylococcus test plate was developed to evaluate antibiotics and antibiotic combinations against Staphylococcus aureus **biofilms**. The 96-well plate had gentamicin, clindamycin, cefazolin, cloxacillin, rifampin, vancomycin, linezolid, ampicillin sublactam, ciprofloxacin, various combinations of the antibiotics, a growth control, and a sterility control. The sensitivity of planktonic and **biofilm** forms of S. aureus to individual and combination agents could be determined within about 48 h. S. aureus was sensitive to multiple antibiotics and antibiotic combinations as planktonic forms, but was significantly more resistant as a **biofilm**.

IT **57-92-1**, Streptomycin
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); PRPH (Prophetic); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(plate for selection of antibiotics and fungicides against **biofilm** infections)

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L59 ANSWER 9 OF 30 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:1278450 HCAPLUS Full-text
DOCUMENT NUMBER: 147:508656
TITLE: Antimicrobial site dressings comprising, for example,

a silver compound for use with percutaneous **medical devices**

INVENTOR(S): McMaken, Jack D.; Gibbins, Bruce L.
PATENT ASSIGNEE(S): Acrymed, Inc., USA
SOURCE: PCT Int. Appl., 22pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007127236	A2	20071108	WO 2007-US9997	20070425
WO 2007127236	A3	20081106		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA				
US 20070293800	A1	20071220	US 2007-789701	20070425
EP 2015722	A2	20090121	EP 2007-755996	20070425
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, RS				

PRIORITY APPLN. INFO.: US 2006-796039P P 20060428
WO 2007-US9997 W 20070425

ED Entered STN: 09 Nov 2007

AB The present invention comprises antimicrobial articles for use with a percutaneous device, comprising a matrix which may contact the percutaneous device in a three-dimensional mode and release antimicrobial agents (e.g., silver ions) to the percutaneous device access site. In addition, the antimicrobial article of the present invention may donate moisture to a dry **dermal** site (e.g., a dry wound bed) and/or absorb liquid or exudates of a **dermal** site. The present invention also comprises methods for treating and/or **preventing** an **infection** using the antimicrobial articles of the present invention. Thus, a silver-containing polyacrylate matrix was made by mixing 185 g acrylamide and 2 g bisacrylamide into 3330 g of water containing 33.3 g of sodium chloride. To this mixture, was added 21 g of guar gum and 188 g of glycerol. After mixing to homogeneity, a solution containing 0.563 g silver nitrate was slowly added to the mixing batch. The polymerization of the mixture was accomplished by blending 1.8 mL TEMED and 2.6 g ammonium persulfate into the mixture The mixture was poured into the appropriate molds before polymerization in a dark place. The gelled polymer was removed from the mold, dehydrated by mild heat and then rehydrated by humidification to a desired moisture content, 22% weight/weight The matrix was then cut to form the article with one or two passages for use with percutaneous devices.

IT **57-92-1**, Streptomycin
RL: TEM (Technical or engineered material use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antimicrobial site dressings for **prevention** of **infection** related to use of percutaneous **medical devices**)

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L59 ANSWER 10 OF 30 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:675678 HCAPLUS Full-text
DOCUMENT NUMBER: 147:87617
TITLE: Use of rifamycins for **treatment** of infections, including **prosthetic** joint infections
INVENTOR(S): Murphy, Christoper K.; Rothstein, David M.
PATENT ASSIGNEE(S): Activbiotics, Inc., USA
SOURCE: PCT Int. Appl., 98pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2007070084	A1	20070621	WO 2006-US18559		20060515
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
AU 2006325493	A1	20070621	AU 2006-325493		20060515
CA 2631954	A1	20070621	CA 2006-2631954		20060515
EP 1971342	A1	20080924	EP 2006-759753		20060515
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR					
US 20070142392	A1	20070621	US 2006-638738		20061214
IN 2008DN05060	A	20080926	IN 2008-DN5060		20080612
MX 2008007809	A	20080915	MX 2008-7809		20080613
CN 101365455	A	20090211	CN 2006-80052335		20080805
PRIORITY APPLN. INFO.:			US 2005-750774P	P	20051215
			WO 2006-US18559	W	20060515

ED Entered STN: 22 Jun 2007
AB The invention provides methods, compns., and kits using rifamycin compds. (Markush included) for treating a variety of bacterial infections, including **prosthetic** joint infections, infections caused by **medical implants**, infectious arthritis, and osteomyelitis. The rifamycin compds. may be used in conjunction with other antibiotics.
IT **57-92-1**, Streptomycin
RL: PAC (Pharmacological activity); TEM (Technical or engineered material use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rifamycins for **treatment** of infections, including **prosthetic** joint infections, and use with other antibiotics)
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L59 ANSWER 11 OF 30 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:169442 HCAPLUS Full-text
DOCUMENT NUMBER: 148:513140
TITLE: Effect of different antimicrobial agents on Staphylococcus aureus adhesiveness and **biofilm** formation
AUTHOR(S): Yassien, M.; Al-Ansari, S.
CORPORATE SOURCE: Faculty of Pharmacy, King Abdul Aziz University, Jeddah, Saudi Arabia
SOURCE: New Egyptian Journal of Microbiology (2006), 13, 29-51
CODEN: NEJMCI; ISSN: 1687-1219
PUBLISHER: Egyptian Society for Biotechnology
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 11 Feb 2008
AB The effect of fluoroquinolones (ciprofloxacin, ofloxacin, and levofloxacin), clindamycin, β-lactams (cefoperazone, cefotaxime, cefepime), streptomycin, and vancomycin on the adherence and **biofilm** formation by Staphylococcus aureus (12 **clin.** isolates) was studied. In the presence of 1/2 MIC, 1/4 MIC and 1/8 MIC, the optical d. of the formed **biofilms** on plastic surfaces was **reduced** to 24-59.9%, 32.4-76.7% and 49.7-88.5% of the controls, resp. **Treatment** of the preformed **biofilms** with high concns. (25-200 μg/mL) of the tested agents caused reduction in the optical d. of the adherent **biofilms** to a range from 52.3 to 87.7% of the control. In an in-vitro model of vascular catheter **colonization** , the tested subinhibitory concns. **reduced** the percentage of the viable adherent cells to 32.1-71.6%, 42.5-85.6%, and 60.3-95.3% of the controls, resp. The tested fluoroquinolones and clindamycin are significantly more active than the other tested agents, and levofloxacin was the most active one. The vascular catheter segments precolonized with S. aureus for 24 h and exposed to 50 μg/mL (4-31 times MIC) of the tested fluoroquinolones and clindamycin for 2 h showed few viable adherent cells (7-13 CFU/segment), while no adherent viable cells were cultured in the presence of 100 μg/mL(8-62 times MIC). Also, the tested subinhibitory concns. **reduced** the percentage of the viable **bacterial** cells adherent to the surface of human lung epithelial A549 cells to the range of 30.1-79.2%, 41.1-89.3%, and 60.9-96.2% of the control, resp. **Treatment** of the A549 cells, preattached with bacterial cells, with the tested agents at concns. of 5, 10, and 20 μg/mL (1/4-50 times MIC) reduced the range of the percentage of the adherent cells to 53.2-88.3%, 33.8-79.2%, and 27.2-68.1% of the control, resp. The superior activity of the tested fluoroquinolones and clindamycin was also observed The obtained data show that subinhibitory concns. of ciprofloxacin, ofloxacin, levofloxacin, and clindamycin efficiently **reduced** the **biofilm** formation and adherence of S. aureus to the surfaces of plastics, vascular catheters, and human lung epithelial A549 cells. Also, higher concns. (≥ MIC) of fluoroquinolones and clindamycin were able to eradicate the adherent S. aureus.
IT **57-92-1**, Streptomycin
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of different antimicrobial agents on Staphylococcus aureus adhesiveness and **biofilm** formation)
REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L59 ANSWER 12 OF 30 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:1126608 HCAPLUS Full-text
DOCUMENT NUMBER: 143:393137
TITLE: Novel modification of medical prostheses by coating with therapeutic agents
INVENTOR(S): Mansouri, Mohammad David; Darouiche, Rabih O.

PATENT ASSIGNEE(S): Baylor College of Medicine, USA
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005096990	A2	20051020	WO 2005-US10944	20050331
WO 2005096990	A3	20070208		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2005231417	A1	20051020	AU 2005-231417	20050331
CA 2561496	A1	20051020	CA 2005-2561496	20050331
US 20050271694	A1	20051208	US 2005-95975	20050331
US 7238363	B2	20070703		
EP 1737378	A2	20070103	EP 2005-731606	20050331
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, LV, MK, YU				

PRIORITY APPLN. INFO.: US 2004-558918P P 20040402
WO 2005-US10944 W 20050331

ED Entered STN: 20 Oct 2005

AB The incorporation of one or more therapeutic agents on metallic and non-metallic medical prostheses is provided. The therapeutic agent can be used, for example, to **prevent**, treat, or **reduce bacterial** and **fungal infections** associated with these implants. Addnl., the therapeutic agents can be used to effect other therapeutic benefits. Specifically, a bilayer therapeutic coating is applied in two steps. Addnl., non-antimicrobial therapeutic agents may be incorporated in this coating to treat, prevent, modify, or stimulate certain clin. bioactivities. Titanium cylinders were coated with a solution containing non-chromated hide powder, rifampin, and minocycline in glacial acetic acid. Antimicrobial activity of the coated device against Staphylococcus **epidermidis**, Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, and Candida albicans was shown.

IT **57-92-1**, Streptomycin, biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel modification of medical prostheses by coating with therapeutic agents)

OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L59 ANSWER 13 OF 30 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:412787 HCAPLUS Full-text
DOCUMENT NUMBER: 140:395549
TITLE: Controlled and continued delivery of rifaximin and/or

other substances
INVENTOR(S): Chiarelli, Piero; Dalseno, Renzo
PATENT ASSIGNEE(S): Italy
SOURCE: PCT Int. Appl., 15 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004041240	A1	20040521	WO 2003-EP12346	20031105
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003276254	A1	20040607	AU 2003-276254	20031105
EP 1560566	A1	20050810	EP 2003-810439	20031105
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
US 20060110447	A1	20060525	US 2005-533768	20050504

PRIORITY APPLN. INFO.:

IT 2002-FI212	A	20021105
IT 2002-MI2438	A	20021118
IT 2003-PI5	A	20030114
IT 2003-PI13	A	20030221
WO 2003-EP12346	W	20031105

ED Entered STN: 21 May 2004
AB A gum-like device is designed for the controlled and continued delivery of rifaximin, without producing the usually intense red coloration, for the resolution of the **infections** and the **reduction** of the inflammation in the oral cavity and in the laryngo-**pharyngeal** one. The device also protects either the gum or the dental apparatus from acute infections, from the infiltration and the stagnation of the food, and fights chronic infections such as in the periodontal pockets. Moreover, the device can be used to protect the gum from the traumatizing collision that the food exercises during the mastication.
IT **57-92-1**, Streptomycin, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(gum-like device for controlled and continued delivery of rifaximin and other substances)
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L59 ANSWER 14 OF 30 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2002:977651 HCAPLUS Full-text
DOCUMENT NUMBER: 138:61381
TITLE: Biofilm degradation or sloughing compositions containing furanones
INVENTOR(S): Kjelleberg, Staffan; Givskov, Michael; Hentzer, Morten
PATENT ASSIGNEE(S): Unisearch Limited, Australia
SOURCE: PCT Int. Appl., 69 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002102370	A1	20021227	WO 2002-AU797	20020618
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002312648	A1	20030102	AU 2002-312648	20020618
US 20040147595	A1	20040729	US 2004-481250	20040331
PRIORITY APPLN. INFO.:			AU 2001-5754 A	20010618
			WO 2002-AU797 W	20020618

OTHER SOURCE(S): MARPAT 138:61381
ED Entered STN: 29 Dec 2002
AB The present invention relates to a method for the regulation and **control** of **biofilm** layers. In particular, the present invention is concerned with methods for degrading or causing sloughing of biofilms from surfaces (e.g., **medical** goods, **implants**, household furnishings, cooling systems in power plants). The invention is also related to compns. suitable for use in carrying out these methods. Thus, halogenated furanones were tested 8 different concns. The inhibitory activity of each compound on the fluorescent phenotype was diminished as the concentration increased.
IT **57-92-1**, Streptomycin, biological studies
RL: PAC (Pharmacological activity); BIOL (Biological study)
(biofilm degradation or sloughing compns. containing furanones)
OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L59 ANSWER 15 OF 30 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2002:241243 HCAPLUS Full-text
DOCUMENT NUMBER: 136:284492
TITLE: Compositions for treating biofilm
INVENTOR(S): Budny, John A.; Budny, Matthew J.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 12 pp., Cont.-in-part of U. S. Ser. No. 587,818.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20020037260	A1	20020328	US 2001-876248	20010606
US 5871714	A	19990216	US 1997-951393	19971016
US 6159447	A	20001212	US 1999-249674	19990212
US 6830745	B1	20041214	US 2000-587818	20000606
PRIORITY APPLN. INFO.:			US 1997-951393 A2	19971016

US 1999-249674 A2 19990212
US 2000-587818 A2 20000606

ED Entered STN: 28 Mar 2002

AB A composition for treating a biofilm structure including a cellular colony and the sessile cells associated with the biofilm structure, comprises an enzyme selected for its ability to dismantle the biofilm structure, an anchor mol. coupled to the enzyme to form an enzyme-anchor complex, the anchor mol. being capable of attaching to a surface on or proximal the biofilm structure, the anchor mol. being selected for its ability to bind to the cellular colony or other bioadhesive mols.. The attachment of the anchor to the surface permits prolonged retention time of the enzyme-anchor complex where the cellular colony and biofilm are present. The first anchor enzyme component degrades biofilm structures and the second anchor enzyme component hase the capability to act directly upon the bacteria for a bactericidal effect.

IT **57-92-1**, Streptomycin, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. for treating **biofilm**)

OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

L59 ANSWER 16 OF 30 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2002:221202 HCAPLUS Full-text
DOCUMENT NUMBER: 136:257216
TITLE: Compositions and methods for treating infections using cationic peptides alone or in combination with antibiotics
INVENTOR(S): Krieger, Timothy J.; Taylor, Robert; Erfle, Douglas; Fraser, Janet R.; West, Michael H. P.; Mcnichol, Patricia J.
PATENT ASSIGNEE(S): Micrologix Biotech, Inc, Can.
SOURCE: U.S. Pat. Appl. Publ., 111 pp., Cont.-in-part of U. S. 6,180,604.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20020035061	A1	20020321	US 1998-30619	19980225
US 6503881	B2	20030107		
US 6180604	B1	20010130	US 1997-915314	19970820
EP 1174439	A2	20020123	EP 2001-119148	19970821
EP 1174439	A3	20030326		
EP 1174439	B1	20081008		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
CA 2282807	A1	19980917	CA 1998-2282807	19980310
AU 9866047	A	19980929	AU 1998-66047	19980310
EP 966481	A2	19991229	EP 1998-907779	19980310
EP 966481	B1	20060719		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002544759	T	20021224	JP 1998-538997	19980310
AT 333464	T	20060815	AT 1998-907779	19980310
ES 2264198	T3	20061216	ES 1998-907779	19980310
HK 1025103	A1	20060929	HK 2000-103705	20000620
US 6538106	B1	20030325	US 2000-667486	20000922
US 20030232750	A1	20031218	US 2002-277233	20021018

US 7309759	B2	20071218			
US 20040009910	A1	20040115	US 2003-351985		20030124
US 7390787	B2	20080624			
JP 2005225857	A	20050825	JP 2004-242925		20040823
JP 4073900	B2	20080409			
US 20080242614	A1	20081002	US 2008-58500		20080328
PRIORITY APPLN. INFO.:			US 1996-24754P	P	19960821
			US 1997-34949P	P	19970113
			US 1997-40649P	P	19970310
			US 1997-915314	A2	19970820
			US 1997-60099P	P	19970926
			EP 1997-941352	A3	19970821
			JP 1998-510994	A3	19970821
			US 1998-30619	A	19980225
			WO 1998-CA190	W	19980310
			US 2000-667486	A1	20000922
			US 2003-351985	A1	20030124

OTHER SOURCE(S): MARPAT 136:257216
ED Entered STN: 22 Mar 2002
AB Compns. and methods for treating infections, especially bacterial infections, are provided. Indolicidin peptide analogs containing at least two basic amino acids are prepared The analogs are administered as modified peptides, preferably containing photo-oxidized solubilizer.
IT **57-92-1**, Streptomycin, biological studies
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. and methods for treating infections using cationic peptides alone or in combination with antibiotics)
OS.CITING REF COUNT: 12 THERE ARE 12 CAPLUS RECORDS THAT CITE THIS RECORD (12 CITINGS)

Text search results: commercial files

=> d L59 17-30 ibib ab hit

L59 ANSWER 17 OF 30 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2008047574 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 17993539
TITLE: **Vibrio** parahaemolyticus ScrC modulates cyclic dimeric GMP regulation of gene expression relevant to growth on surfaces.
AUTHOR: Ferreira Rosana B R; Antunes Luis Caetano M; Greenberg E Peter; McCarter Linda L
CORPORATE SOURCE: Department of Microbiology, The University of Iowa, Iowa City, Iowa 52242, USA.
SOURCE: Journal of bacteriology, (2008 Feb) Vol. 190, No. 3, pp. 851-60. Electronic Publication: 2007-11-09.
Journal code: 2985120R. E-ISSN: 1098-5530.
Report No.: NLM-PMC2223563.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200802
ENTRY DATE: Entered STN: 19 Jan 2008
Last Updated on STN: 13 Feb 2008
Entered Medline: 12 Feb 2008

AB In **Vibrio** parahaemolyticus, scrC participates in controlling the decision to be a highly mobile swarmer cell or a more adhesive, **biofilm**-proficient cell type. scrC mutants display decreased swarming motility over surfaces and enhanced capsular polysaccharide production. ScrC is a cytoplasmic **membrane** protein that contains both GGDEF and EAL conserved protein domains. These domains have been shown in many organisms to respectively control the formation and degradation of the small signaling nucleotide cyclic dimeric GMP (**c-di-GMP**). The scrC gene is part of the three-gene scrABC operon. Here we report that this operon influences the cellular nucleotide pool and that **c-di-GMP** levels inversely modulate lateral flagellar and capsular polysaccharide gene expression. High concentrations of this nucleotide prevent swarming and promote adhesiveness. Further, we demonstrate that ScrC has intrinsic diguanylate cyclase and phosphodiesterase activities, and these activities are controlled by ScrAB. Specifically, ScrC acts to form **c- di-GMP** in the absence of ScrA and ScrB; whereas ScrC acts to degrade **c-di-GMP** in the presence of ScrA and ScrB. The scrABC operon is specifically induced by growth on a surface, and the analysis of mutant phenotypes supports a model in which the phosphodiesterase activity of ScrC plays a dominant role during surface translocation and in **biofilms**.

TI **Vibrio** parahaemolyticus ScrC modulates cyclic dimeric GMP regulation of gene expression relevant to growth on surfaces.

AB In **Vibrio** parahaemolyticus, scrC participates in controlling the decision to be a highly mobile swarmer cell or a more adhesive, **biofilm**-proficient cell type. scrC mutants display decreased swarming motility over surfaces and enhanced capsular polysaccharide production. ScrC is a cytoplasmic **membrane** protein that contains both GGDEF and EAL conserved protein domains. These domains have been shown in many organisms to respectively control the formation and degradation of the small signaling nucleotide cyclic dimeric GMP (**c-di-GMP**). The scrC gene is part of the three-gene scrABC operon. Here we report that this operon influences the cellular nucleotide pool and that **c-di-GMP** levels inversely modulate lateral flagellar and capsular polysaccharide gene expression. High concentrations of this nucleotide prevent swarming and

promote adhesiveness. Further, we demonstrate that ScrC has intrinsic diguanylate cyclase and phosphodiesterase activities, and these activities are controlled by ScrAB. Specifically, ScrC acts to form **c- di-GMP** in the absence of ScrA and ScrB; whereas ScrC acts to degrade **c-di-GMP** in the presence of ScrA and ScrB. The scrABC operon is specifically induced by growth on a surface, and the analysis of mutant phenotypes supports a model in which the phosphodiesterase activity of ScrC plays a dominant role during surface translocation and in **biofilms.**

CT Bacterial Adhesion
Bacterial Capsules: GE, genetics
Bacterial Capsules: ME, metabolism
Bacterial Proteins: CH, chemistry
Bacterial Proteins: GE, genetics
*Bacterial Proteins: ME, metabolism
Cyclic GMP: ME, metabolism
***Cyclic GMP: PD, pharmacology**
Dimerization
Flagella: GE, genetics
Flagella: ME, metabolism
*Gene Expression Regulation, Bacterial
Membrane Proteins: CH, chemistry
Membrane Proteins: GE, genetics
***Membrane Proteins: ME, metabolism**
Mutation
Operon
Phosphoric Diester Hydrolases: CH, chemistry
Phosphoric Diester Hydrolases: GE, genetics
Phosphoric Diester Hydrolases: ME, metabolism
Phosphorus-Oxygen Lyases: CH, chemistry
Phosphorus-Oxygen Lyases: GE, genetics
Phosphorus-Oxygen Lyases: ME, metabolism
Vibrio parahaemolyticus: GE, genetics
***Vibrio parahaemolyticus: GD, growth & development**
Vibrio parahaemolyticus: ME, metabolism

RN **7665-99-8 (Cyclic GMP)**
CN 0 (Bacterial Capsules); 0 (Bacterial Proteins); 0 (**Membrane** Proteins); EC 3.1.4.- (Phosphoric Diester Hydrolases); EC 4.6.- (Phosphorus-Oxygen Lyases); EC 4.6.1.- (diguanylate cyclase)

L59 ANSWER 18 OF 30 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2007303807 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 17474125
TITLE: Development of nitric oxide synthase-defined neurons in the sea urchin larval ciliary band and evidence for a chemosensory function during metamorphosis.
AUTHOR: Bishop Cory D; Brandhorst Bruce P
CORPORATE SOURCE: Kewalo Marine Laboratories, University of Hawaii, Honolulu, Hawaii, USA.. cdbishop@dal.ca
SOURCE: Developmental dynamics : an official publication of the American Association of Anatomists, (2007 Jun) Vol. 236, No. 6, pp. 1535-46.
Journal code: 9201927. ISSN: 1058-8388.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200708
ENTRY DATE: Entered STN: 23 May 2007
Last Updated on STN: 25 Aug 2007

Entered Medline: 24 Aug 2007

AB We previously reported that initiation of metamorphosis of larvae of Lytechinus pictus is negatively regulated by nitric oxide (NO) and **cGMP**. We have examined the expression of nitric oxide synthase (NOS) and **cGMP** in cells of the developing larva. A section of the post-oral ciliary band of feeding larvae includes neural cells defined by their expression of both NOS and the echinoderm neural-specific antibody 1E11. These neurons project processes to the pre-oral neuropile during larval development. Larvae regenerated this section of the ciliary band after its excision, complete with NOS-defined neurons that projected again to the pre-oral neuropile. Excision of ectoderm containing the post-oral ciliary band prevented a behavioral and morphogenetic response of competent larvae to **biofilm**, and **delayed** initiation of metamorphosis. Elevated **cGMP** levels were detected in several larval and juvenile cell types prior to metamorphosis. **Treatment** of larvae with ODQ, an inhibitor of soluble guanylate cyclase, decreased **cGMP** levels and induced metamorphosis while a generator of NO counteracted this effect, indicating inhibition of metamorphosis by NO operates via interaction with soluble guanylate cyclase. We discuss these observations, proposing that the NOS-defined neurons in the post-oral ciliary band have a chemosensory function during settlement and metamorphosis that involves morphologically specialized ectoderm and manipulation of fluid flow. We provide a tentative cellular model of how environmental signals may be transduced into a metamorphic response. Copyright 2007 Wiley-Liss, Inc.

AB We previously reported that initiation of metamorphosis of larvae of Lytechinus pictus is negatively regulated by nitric oxide (NO) and **cGMP**. We have examined the expression of nitric oxide synthase (NOS) and **cGMP** in cells of the developing larva. A section of the post-oral ciliary band of feeding larvae includes neural cells defined by their expression of both NOS and the echinoderm neural-specific antibody 1E11. These neurons project processes to the pre-oral neuropile during larval development. Larvae regenerated this section of the ciliary band after its excision, complete with NOS-defined neurons that projected again to the pre-oral neuropile. Excision of ectoderm containing the post-oral ciliary band prevented a behavioral and morphogenetic response of competent larvae to **biofilm**, and **delayed** initiation of metamorphosis. Elevated **cGMP** levels were detected in several larval and juvenile cell types prior to metamorphosis. **Treatment** of larvae with ODQ, an inhibitor of soluble guanylate cyclase, decreased **cGMP** levels and induced metamorphosis while a generator of NO counteracted this effect, indicating inhibition of metamorphosis by NO operates via interaction with soluble guanylate cyclase. We discuss these observations, proposing that the NOS-defined neurons in the post-oral ciliary band have a chemosensory function during settlement and metamorphosis that involves morphologically specialized ectoderm and manipulation of fluid flow. We provide a tentative cellular model of how environmental signals may be transduced into a metamorphic response. Copyright 2007 Wiley-Liss, Inc.

CT Aging: PH, physiology
Animals
Biofilms
*Chemotaxis
Cyclic GMP: ME, metabolism
Gene Expression Regulation, Developmental
Larva: CY, cytology
Larva: EN, enzymology
Larva: GD, growth & development
*Metamorphosis, Biological
Mouth: EN, enzymology
Mouth: GD, growth & development
*Neurons: CY, cytology
*Neurons: EN, enzymology
Nitric Oxide Synthase: GE, genetics

*Nitric Oxide Synthase: ME, metabolism
Sea Urchins: CY, cytology
*Sea Urchins: EN, enzymology
Sea Urchins: GE, genetics
*Sea Urchins: GD, growth & development
Signal Transduction
RN **7665-99-8 (Cyclic GMP)**

L59 ANSWER 19 OF 30 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2008051556 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 18028314
TITLE: Subcellular location characteristics of the Pseudomonas aeruginosa GGDEF protein, WspR, indicate that it produces cyclic-di-GMP in response to growth on surfaces.
AUTHOR: Guvener Zehra Tuzun; Harwood Caroline S
CORPORATE SOURCE: Department of Microbiology, University of Washington, Seattle, WA 98195, USA.
CONTRACT NUMBER: GM56665 (United States NIGMS NIH HHS)
SOURCE: Molecular microbiology, (2007 Dec) Vol. 66, No. 6, pp. 1459-73. Electronic Publication: 2007-11-19.
Journal code: 8712028. ISSN: 0950-382X.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200806
ENTRY DATE: Entered STN: 23 Jan 2008
Last Updated on STN: 14 Jun 2008
Entered Medline: 13 Jun 2008

AB The Pseudomonas aeruginosa Wsp signal transduction system produces cyclic-di-GMP (**c-di-GMP**), an intracellular messenger that stimulates **biofilm** formation and suppresses motility. The Wsp system is homologous to chemotaxis systems and includes a **membrane**-bound receptor protein, WspA, and a response regulator GGDEF protein, WspR, that catalyses **c-di- GMP** synthesis when phosphorylated. We found that the subcellular distributions of fluorescent protein-tagged WspA and WspR differed markedly from their chemotaxis counterparts. WspA-YFP formed patches in cells whereas WspR-YFP was dispersed when unphosphorylated and formed bright cytoplasmic clusters when phosphorylated. WspR formed clusters in cells of a DeltawspF mutant, a genetic background that causes constitutive phosphorylation of WspR, but was dispersed in cells of a wspA mutant, a genetic background necessary for WspR phosphorylation. In addition, WspR mutated at Asp70, its predicted site of phosphorylation, did not form clusters. **C-di-GMP** synthesis was not required for cluster formation. WspR-YFP was dispersed in liquid-grown wild-type cells, but formed clusters that sometimes appeared and disappeared over the course of a few minutes in cells grown on an agar surface. Our results suggest that the compartmentalized production of **c-di-GMP** in response to a stimulus associated with growth on a surface is an important functional characteristic of the Wsp system.
AB The Pseudomonas aeruginosa Wsp signal transduction system produces cyclic-di-GMP (**c-di-GMP**), an intracellular messenger that stimulates **biofilm** formation and suppresses motility. The Wsp system is homologous to chemotaxis systems and includes a **membrane**-bound receptor protein, WspA, and a response regulator GGDEF protein, WspR, that catalyses **c-di- GMP** synthesis when phosphorylated. We found that the subcellular distributions of fluorescent protein-tagged WspA and WspR differed markedly from their chemotaxis counterparts. WspA-YFP formed patches in cells whereas WspR-YFP was dispersed when unphosphorylated and formed bright cytoplasmic clusters when phosphorylated. WspR formed clusters in cells of a DeltawspF mutant, a genetic background that causes constitutive phosphorylation of WspR, but was dispersed in cells of a wspA

mutant, a genetic background necessary for WspR phosphorylation. In addition, WspR mutated at Asp70, its predicted site of phosphorylation, did not form clusters. **C-di-GMP** synthesis was not required for cluster formation. WspR-YFP was dispersed in liquid-grown wild-type cells, but formed clusters that sometimes appeared and disappeared over the course of a few minutes in cells grown on an agar surface. Our results suggest that the compartmentalized production of **c-di-GMP** in response to a stimulus associated with growth on a surface is an important functional characteristic of the Wsp system.

CT Bacterial Proteins: GE, genetics
*Bacterial Proteins: ME, metabolism
***Cyclic GMP: AA, analogs & derivatives**
Cyclic GMP: ME, metabolism
Cytoplasm: ME, metabolism
Microscopy, Fluorescence
Models, Biological
Mutagenesis, Site-Directed
Mutation
Phosphorylation
Pseudomonas aeruginosa: GE, genetics
*Pseudomonas aeruginosa: ME, metabolism
Recombinant Fusion Proteins: GE, genetics
*Recombinant Fusion Proteins: ME, metabolism
Signal Transduction: GE, genetics
Signal Transduction: PH, physiology

RN **61093-23-0 (bis(3',5')-cyclic diguanylic acid); 7665-99-8 (Cyclic GMP)**

L59 ANSWER 20 OF 30 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2006671047 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 16980460
TITLE: Diguanylate cyclases control magnesium-dependent motility of **Vibrio** fischeri.
AUTHOR: O'Shea Therese M; Klein Adam H; Geszvain Kati; Wolfe Alan J; Visick Karen L
CORPORATE SOURCE: Department of Microbiology and Immunology, Loyola University Chicago, 2160 S. First Ave., Bldg. 105, Maywood, IL 60153, USA.
CONTRACT NUMBER: GM066130 (United States NIGMS NIH HHS)
GM59690 (United States NIGMS NIH HHS)
SOURCE: Journal of bacteriology, (2006 Dec) Vol. 188, No. 23, pp. 8196-205. Electronic Publication: 2006-09-15.
Journal code: 2985120R. ISSN: 0021-9193.
Report No.: NLM-PMC1698204.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200612
ENTRY DATE: Entered STN: 21 Nov 2006
Last Updated on STN: 28 Dec 2006
Entered Medline: 27 Dec 2006

AB Flagellar biogenesis and hence motility of **Vibrio** fischeri depends upon the presence of magnesium. In the absence of magnesium, cells contain few or no flagella and are poorly motile or nonmotile. To dissect the mechanism by which this regulation occurs, we screened transposon insertion mutants for those that could migrate through soft agar medium lacking added magnesium. We identified mutants with insertions in two distinct genes, VF0989 and VFA0959, which we termed mifA and mifB, respectively, for magnesium-dependent induction

of flagellation. Each gene encodes a predicted **membrane**-associated protein with diguanylate cyclase activity. Consistent with that activity, introduction into V. fischeri of medium-copy plasmids carrying these genes inhibited motility. Furthermore, multicopy expression of mifA induced other phenotypes known to be correlated with diguanylate cyclase activity, including cellulose biosynthesis and **biofilm** formation. To directly test their function, we introduced the wild-type genes on high-copy plasmids into Escherichia coli. We assayed for the production of cyclic di-GMP using two-dimensional thin-layer chromatography and found that strains carrying these plasmids produced a small but reproducible spot that migrated with an R(f) value consistent with cyclic di-GMP that was not produced by strains carrying the vector control. Disruptions of mifA or mifB increased flagellin levels, while multicopy expression decreased them. Semiquantitative reverse transcription-PCR experiments revealed no significant difference in the amount of flagellin transcripts produced in either the presence or absence of Mg(2+) by either vector control or mifA-overexpressing cells, indicating that the impact of magnesium and cyclic-di-GMP primarily acts following transcription. Finally, we present a model for the roles of magnesium and cyclic di-GMP in the control of motility of V. fischeri.

TI Diguanylate cyclases control magnesium-dependent motility of **Vibrio** fischeri.

AB Flagellar biogenesis and hence motility of **Vibrio** fischeri depends upon the presence of magnesium. In the absence of magnesium, cells contain few or no flagella and are poorly motile or nonmotile. To dissect the mechanism by which this regulation occurs, we screened transposon insertion mutants for those that could migrate through soft agar medium lacking added magnesium. We identified mutants with insertions in two distinct genes, VF0989 and VFA0959, which we termed mifA and mifB, respectively, for magnesium-dependent induction of flagellation. Each gene encodes a predicted **membrane**-associated protein with diguanylate cyclase activity. Consistent with that activity, introduction into V. fischeri of medium-copy plasmids carrying these genes inhibited motility. Furthermore, multicopy expression of mifA induced other phenotypes known to be correlated with diguanylate cyclase activity, including cellulose biosynthesis and **biofilm** formation. To directly test their function, we introduced the wild-type genes on high-copy plasmids into Escherichia coli. We assayed for the production of cyclic di-GMP using two-dimensional thin-layer chromatography and found that strains carrying these plasmids produced a small but reproducible spot that migrated with an R(f) value consistent with cyclic di-GMP that was not produced by strains carrying the vector control. Disruptions of mifA or mifB increased flagellin levels, while multicopy expression decreased them. Semiquantitative reverse transcription-PCR experiments revealed no significant difference in the amount of flagellin transcripts produced in either the presence or absence of Mg(2+) by either vector control or mifA-overexpressing cells, indicating that the impact of magnesium and cyclic-di-GMP primarily acts following transcription. Finally, we present a model for the roles of magnesium and cyclic di-GMP in the control of motility of V. fischeri.

CT Bacterial Proteins: GE, genetics
*Bacterial Proteins: PH, physiology
Biofilms: DE, drug effects
Cellulose: BI, biosynthesis
Cyclic GMP: PH, physiology
*Down-Regulation
Escherichia coli: GE, genetics
Escherichia coli: ME, metabolism
Flagella
*Gene Expression Regulation, Bacterial
Genetic Vectors
Locomotion
*Magnesium: PH, physiology

Mutagenesis, Insertional
Phosphorus-Oxygen Lyases: GE, genetics
*Phosphorus-Oxygen Lyases: PH, physiology
Plasmids
Transfection
Vibrio fischeri: GE, genetics
***Vibrio fischeri: PH, physiology**
RN 7439-95-4 (Magnesium); **7665-99-8 (Cyclic GMP)**; 9004-34-6 (Cellulose)

L59 ANSWER 21 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2009181697 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 19218451
TITLE: LapD is a bis-(3',5')-cyclic dimeric GMP-binding protein that regulates surface attachment by Pseudomonas fluorescens Pf0-1.
AUTHOR: Newell Peter D; Monds Russell D; O'Toole George A
CORPORATE SOURCE: Department of Microbiology and Immunology, Dartmouth Medical School, Hanover, NH 03755, USA.
CONTRACT NUMBER: T32 GM08704 (United States NIGMS NIH HHS)
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (2009 Mar 3) Vol. 106, No. 9, pp. 3461-6. Electronic Publication: 2009-02-13.
Journal code: 7505876. E-ISSN: 1091-6490.
Report No.: NLM-PMC2651287.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200904
ENTRY DATE: Entered STN: 5 Mar 2009
Last Updated on STN: 2 Apr 2009
Entered Medline: 1 Apr 2009

AB The second messenger cyclic dimeric GMP (**c-di- GMP**) regulates surface attachment and **biofilm** formation by many bacteria. For Pseudomonas fluorescens Pf0-1, **c- di-GMP** impacts the secretion and localization of the adhesin LapA, which is absolutely required for stable surface attachment and **biofilm** formation by this bacterium. In this study we characterize LapD, a unique **c-di-GMP** effector protein that **controls biofilm** formation by communicating intracellular **c-di-GMP** levels to the **membrane**-localized attachment machinery via its periplasmic domain. LapD contains degenerate and enzymatically inactive diguanylate cyclase and **c-di-GMP** phosphodiesterase (EAL) domains and binds to **c-di- GMP** through a degenerate EAL domain. We present evidence that LapD utilizes an inside-out signaling mechanism: binding **c- di-GMP** in the cytoplasm and communicating this signal to the periplasm via its periplasmic domain. Furthermore, we show that LapD serves as the **c-di-GMP** receptor connecting environmental modulation of intracellular **c-di- GMP** levels by inorganic phosphate to regulation of LapA localization and thus surface commitment by P. fluorescens.
AB The second messenger cyclic dimeric GMP (**c-di- GMP**) regulates surface attachment and **biofilm** formation by many bacteria. For Pseudomonas fluorescens Pf0-1, **c- di-GMP** impacts the secretion and localization of the adhesin LapA, which is absolutely required for stable surface attachment and **biofilm** formation by this bacterium. In this study we characterize LapD, a unique **c-di-GMP** effector protein that **controls biofilm** formation by communicating intracellular **c-di-GMP** levels to the **membrane**-localized attachment machinery via its periplasmic domain. LapD contains degenerate and enzymatically inactive diguanylate cyclase and **c-di-GMP** phosphodiesterase

(EAL) domains and binds to **c-di- GMP** through a degenerate EAL domain. We present evidence that LapD utilizes an inside-out signaling mechanism: binding **c- di-GMP** in the cytoplasm and communicating this signal to the periplasm via its periplasmic domain. Furthermore, we show that LapD serves as the **c-di-GMP** receptor connecting environmental modulation of intracellular **c-di- GMP** levels by inorganic phosphate to regulation of LapA localization and thus surface commitment by P. fluorescens.

CT **3',5'-Cyclic-GMP Phosphodiesterases: ME, metabolism**
Adhesins, Bacterial: ME, metabolism
*Bacterial Adhesion
Carrier Proteins: GE, genetics
*Carrier Proteins: ME, metabolism
Cyclic GMP: AA, analogs & derivatives
Cyclic GMP: ME, metabolism
Enzyme Activation
Intracellular Signaling Peptides and Proteins: GE, genetics
*Intracellular Signaling Peptides and Proteins: ME, metabolism
Mutation: GE, genetics
Protein Binding
*Protein Multimerization
Pseudomonas fluorescens: GE, genetics
*Pseudomonas fluorescens: ME, metabolism
Signal Transduction

RN **61093-23-0 (bis(3',5')-cyclic diguanylic acid); 7665-99-8 (Cyclic GMP)**

CN 0 (Adhesins, Bacterial); 0 (Carrier Proteins); 0 (Intracellular Signaling Peptides and Proteins); 0 (**cyclic GMP**-binding protein); EC 3.1.4.35 (3',5'-**Cyclic-GMP** Phosphodiesterases)

L59 ANSWER 22 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2009444210 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 19460094
TITLE: Second messenger signalling governs Escherichia coli **biofilm** induction upon ribosomal stress.
AUTHOR: Boehm Alex; Steiner Samuel; Zaehringer Franziska; Casanova Alain; Hamburger Fabienne; Ritz Daniel; Keck Wolfgang; Ackermann Martin; Schirmer Tilman; Jenal Urs
CORPORATE SOURCE: Biozentrum, University of Basel, Klingelbergstrasse 50/70, 4056 Basel, Switzerland.. alexander.boehm@unibas.ch
SOURCE: Molecular microbiology, (2009 Jun) Vol. 72, No. 6, pp. 1500-16. Electronic Publication: 2009-05-15. Journal code: 8712028. E-ISSN: 1365-2958.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T) (RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200907
ENTRY DATE: Entered STN: 27 Jun 2009
Last Updated on STN: 22 Jul 2009
Entered Medline: 21 Jul 2009

AB **Biofilms** are communities of surface-attached, matrix-embedded microbial cells that can resist antimicrobial chemotherapy and contribute to persistent infections. Using an Escherichia coli **biofilm** model we found that exposure of bacteria to subinhibitory concentrations of ribosome-targeting antibiotics leads to strong **biofilm** induction. We present evidence that this effect is elicited by the ribosome in response to translational stress. **Biofilm** induction involves upregulation of the polysaccharide adhesin poly-beta-1,6-N-

acetyl-glucosamine (poly-GlcNAc) and two components of the poly-GlcNAc biosynthesis machinery, PgaA and PgaD. Poly-GlcNAc **control** depends on the **bacterial** signalling molecules guanosine-bis 3', 5'(diphosphate) (ppGpp) and bis-(**3'-5 '**)-**cyclic di-GMP** (**c-di-GMP**). **Treatment** with translation inhibitors causes a ppGpp hydrolase (SpoT)-mediated reduction of ppGpp levels, resulting in specific derepression of PgaA. Maximal induction of PgaD and poly-GlcNAc synthesis requires the production of **c-di-GMP** by the dedicated diguanylate cyclase YdeH. Our results identify a novel regulatory mechanism that relies on ppGpp signalling to relay information about ribosomal performance to the Pga machinery, thereby inducing adhesin production and **biofilm** formation. Based on the important synergistic roles of ppGpp and **c-di-GMP** in this process, we suggest that interference with bacterial second messenger signalling might represent an effective means for **biofilm control** during chronic **infections**.

TI Second messenger signalling governs Escherichia coli **biofilm** induction upon ribosomal stress.

AB **Biofilms** are communities of surface-attached, matrix-embedded microbial cells that can resist antimicrobial chemotherapy and contribute to persistent infections. Using an Escherichia coli **biofilm** model we found that exposure of bacteria to subinhibitory concentrations of ribosome-targeting antibiotics leads to strong **biofilm** induction. We present evidence that this effect is elicited by the ribosome in response to translational stress. **Biofilm** induction involves upregulation of the polysaccharide adhesin poly-beta-1,6-N-acetyl-glucosamine (poly-GlcNAc) and two components of the poly-GlcNAc biosynthesis machinery, PgaA and PgaD. Poly-GlcNAc **control** depends on the **bacterial** signalling molecules guanosine-bis 3', 5'(diphosphate) (ppGpp) and bis-(**3'-5 '**)-**cyclic di-GMP** (**c-di-GMP**). **Treatment** with translation inhibitors causes a ppGpp hydrolase (SpoT)-mediated reduction of ppGpp levels, resulting in specific derepression of PgaA. Maximal induction of PgaD and poly-GlcNAc synthesis requires the production of **c-di-GMP** by the dedicated diguanylate cyclase YdeH. Our results identify a novel regulatory mechanism that relies on ppGpp signalling to relay information about ribosomal performance to the Pga machinery, thereby inducing adhesin production and **biofilm** formation. Based on the important synergistic roles of ppGpp and **c-di-GMP** in this process, we suggest that interference with bacterial second messenger signalling might represent an effective means for **biofilm control** during chronic **infections**.

CT Adhesins, Bacterial: ME, metabolism
Anti-Bacterial Agents: PD, pharmacology
***Biofilms: GD, growth & development**
***Cyclic GMP: AA, analogs & derivatives**
Cyclic GMP: ME, metabolism
Escherichia coli: DE, drug effects
Escherichia coli: GE, genetics
Escherichia coli: ME, metabolism
*Escherichia coli: PH, physiology
Escherichia coli Proteins: GE, genetics
Escherichia coli Proteins: ME, metabolism
Gene Expression Regulation, Bacterial
*Guanosine Tetraphosphate: ME, metabolism
Phosphorus-Oxygen Lyases: GE, genetics
Phosphorus-Oxygen Lyases: ME, metabolism
Protein Biosynthesis: DE, drug effects
Pyrophosphatases: GE, genetics
Pyrophosphatases: ME, metabolism
RNA Processing, Post-Transcriptional
*Ribosomes: DE, drug effects
*Second Messenger Systems
beta-Glucans: ME, metabolism

RN 33503-72-9 (Guanosine Tetraphosphate); **61093-23-0 (bis(3',5')-cyclic**

diguanylic acid); 7665-99-8 (Cyclic GMP)

L59 ANSWER 23 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2009124691 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 19088322
TITLE: MucR, a novel **membrane**-associated regulator of alginate biosynthesis in Pseudomonas aeruginosa.
AUTHOR: Hay Iain D; Remminghorst Uwe; Rehm Bernd H A
CORPORATE SOURCE: Institute of Molecular Biosciences, Massey University, Private Bag 11222, Palmerston North, New Zealand.
SOURCE: Applied and environmental microbiology, (2009 Feb) Vol. 75, No. 4, pp. 1110-20. Electronic Publication: 2008-12-16. Journal code: 7605801. E-ISSN: 1098-5336. Report No.: NLM-PMC2643583.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200902
ENTRY DATE: Entered STN: 10 Feb 2009
Last Updated on STN: 24 Feb 2009
Entered Medline: 20 Feb 2009

AB Alginate biosynthesis by Pseudomonas aeruginosa was shown to be regulated by the intracellular second messenger bis-(3'-5')-cyclic-dimeric-GMP (**c-di-GMP**), and binding of **c- di-GMP** to the **membrane** protein Alg44 was required for alginate production. In this study, PA1727, a **c- di-GMP**-synthesizing enzyme was functionally analyzed and identified to be involved in regulation of alginate production. Deletion of the PA1727 gene in the mucoid alginate-overproducing P. aeruginosa strain PDO300 resulted in a nonmucoid phenotype and an about 38-fold decrease in alginate production; thus, this gene is designated mucR. The mucoid alginate-overproducing phenotype was restored by introducing the mucR gene into the isogenic DeltamucR mutant. Moreover, transfer of the MucR-encoding plasmid into strain PDO300 led to an about sevenfold increase in alginate production, wrinkly colony morphology, increased pellicle formation, auto-aggregation, and the formation of highly structured **biofilms** as well as the **inhibition** of swarming motility. Outer **membrane** protein profile analysis showed that overproduction of MucR mediates a strong reduction in the copy number of FliC (flagellin), required for flagellum-mediated motility. Translational reporter enzyme fusions with LacZ and PhoA suggested that MucR is located in the cytoplasmic **membrane** with a cytosolic C terminus. Deletion of the proposed C-terminal GGDEF domain abolished MucR function. MucR was purified and identified using tryptic peptide fingerprinting and matrix-assisted laser desorption ionization-time of flight mass spectrometry. Overall, experimental evidence was provided suggesting that MucR specifically regulates alginate biosynthesis by activation of alginate production through generation of a localized **c-di-GMP** pool in the vicinity of Alg44.

TI MucR, a novel **membrane**-associated regulator of alginate biosynthesis in Pseudomonas aeruginosa.

AB Alginate biosynthesis by Pseudomonas aeruginosa was shown to be regulated by the intracellular second messenger bis-(3'-5')-cyclic-dimeric-GMP (**c-di-GMP**), and binding of **c- di-GMP** to the **membrane** protein Alg44 was required for alginate production. In this study, PA1727, a **c- di-GMP**-synthesizing enzyme was functionally analyzed and identified to be involved in regulation of alginate production. Deletion of the PA1727 gene in the mucoid alginate-overproducing P. aeruginosa strain PDO300 resulted in a nonmucoid phenotype and an about 38-fold decrease in alginate production; thus, this gene is designated mucR. The mucoid alginate-overproducing phenotype was restored by introducing the mucR gene into the isogenic DeltamucR mutant. Moreover,

transfer of the MucR-encoding plasmid into strain PDO300 led to an about sevenfold increase in alginate production, wrinkly colony morphology, increased pellicle formation, auto-aggregation, and the formation of highly structured **biofilms** as well as the **inhibition** of swarming motility. Outer **membrane** protein profile analysis showed that overproduction of MucR mediates a strong reduction in the copy number of FliC (flagellin), required for flagellum-mediated motility. Translational reporter enzyme fusions with LacZ and PhoA suggested that MucR is located in the cytoplasmic **membrane** with a cytosolic C terminus. Deletion of the proposed C-terminal GGDEF domain abolished MucR function. MucR was purified and identified using tryptic peptide fingerprinting and matrix-assisted laser desorption ionization-time of flight mass spectrometry. Overall, experimental evidence was provided suggesting that MucR specifically regulates alginate biosynthesis by activation of alginate production through generation of a localized **c-di-GMP** pool in the vicinity of Alg44.

CT Alginates
Alkaline Phosphatase: GE, genetics
Alkaline Phosphatase: ME, metabolism
Bacterial Outer Membrane Proteins: AN, analysis
Bacterial Proteins: GE, genetics
Bacterial Proteins: IP, isolation & purification
*Bacterial Proteins: PH, physiology
Cell Membrane: CH, chemistry
Cyclic GMP: AA, analogs & derivatives
Cyclic GMP: ME, metabolism
Gene Deletion
*Gene Expression Regulation, Bacterial
Genes, Reporter
Genetic Complementation Test
Glucuronic Acid: BI, biosynthesis
Hexuronic Acids
Locomotion
Pseudomonas aeruginosa: CH, chemistry
Pseudomonas aeruginosa: GE, genetics
Pseudomonas aeruginosa: ME, metabolism
*Pseudomonas aeruginosa: PH, physiology
Recombinant Fusion Proteins: GE, genetics
Recombinant Fusion Proteins: ME, metabolism
Spectrometry, Mass, Matrix-Assisted Laser Desorption-Ionization
beta-Galactosidase: GE, genetics
beta-Galactosidase: ME, metabolism

RN 576-37-4 (Glucuronic Acid); **61093-23-0 (bis(3',5')-cyclic diguanylic acid)**; **7665-99-8 (Cyclic GMP)**; 9005-32-7 (alginic acid)

CN 0 (Alginates); 0 (Bacterial Outer **Membrane** Proteins); 0 (Bacterial Proteins); 0 (Hexuronic Acids); 0 (Recombinant Fusion Proteins); EC 3.1.3.1 (Alkaline Phosphatase); EC 3.2.1.23 (beta-Galactosidase)

L59 ANSWER 24 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2008457940 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 18502872
TITLE: A **staphylococcal** GGDEF domain protein regulates **biofilm** formation independently of cyclic dimeric GMP.
AUTHOR: Holland Linda M; O'Donnell Sinead T; Ryjenkov Dmitri A; Gomelsky Larissa; Slater Shawn R; Fey Paul D; Gomelsky Mark; O'Gara James P
CORPORATE SOURCE: School of Biomolecular and Biomedical Science, Ardmore House, University College Dublin, Belfield, Dublin 4, Ireland.

CONTRACT NUMBER: AI49311 (United States NIAID NIH HHS)
SOURCE: Journal of bacteriology, (2008 Aug) Vol. 190, No. 15, pp. 5178-89. Electronic Publication: 2008-05-23.
Journal code: 2985120R. E-ISSN: 1098-5530.
Report No.: NLM-PMC2493275.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200808
ENTRY DATE: Entered STN: 19 Jul 2008
Last Updated on STN: 13 Aug 2008
Entered Medline: 12 Aug 2008

AB Cyclic dimeric GMP (**c-di-GMP**) is an important **biofilm** regulator that allosterically activates enzymes of exopolysaccharide biosynthesis. Proteobacterial genomes usually encode multiple GGDEF domain-containing diguanylate cyclases responsible for **c-di-GMP** synthesis. In contrast, only one conserved GGDEF domain protein, GdpS (for GGDEF domain protein from **Staphylococcus**), and a second protein with a highly modified GGDEF domain, GdpP, are present in the sequenced **staphylococcal** genomes. Here, we investigated the role of GdpS in **biofilm** formation in **Staphylococcus epidermidis** . Inactivation of gdpS impaired **biofilm** formation in medium supplemented with NaCl under static and flow-cell conditions, whereas gdpS overexpression complemented the mutation and enhanced wild-type **biofilm** development. GdpS increased production of the icaADBC-encoded exopolysaccharide, poly-N-acetyl-glucosamine, by elevating icaADBC mRNA levels. Unexpectedly, **c-di-GMP** synthesis was found to be irrelevant for the ability of GdpS to elevate icaADBC expression. Mutagenesis of the GGEEF motif essential for diguanylate cyclase activity did not impair GdpS, and the N-terminal fragment of GdpS lacking the GGDEF domain partially complemented the gdpS mutation. Furthermore, heterologous diguanylate cyclases expressed in trans failed to complement the gdpS mutation, and the purified GGDEF domain from GdpS possessed no diguanylate cyclase activity in vitro. The gdpS gene from **Staphylococcus** aureus exhibited similar characteristics to its S. **epidermidis** ortholog, suggesting that the GdpS-mediated signal transduction is conserved in **staphylococci**. Therefore, GdpS affects **biofilm** formation through a novel **c-di-GMP** -independent mechanism involving increased icaADBC mRNA levels and exopolysaccharide biosynthesis. Our data raise the possibility that **staphylococci** cannot synthesize **c-di- GMP** and have only remnants of a **c-di- GMP** signaling pathway.

TI A **staphylococcal** GGDEF domain protein regulates **biofilm** formation independently of cyclic dimeric GMP.

AB Cyclic dimeric GMP (**c-di-GMP**) is an important **biofilm** regulator that allosterically activates enzymes of exopolysaccharide biosynthesis. Proteobacterial genomes usually encode multiple GGDEF domain-containing diguanylate cyclases responsible for **c-di-GMP** synthesis. In contrast, only one conserved GGDEF domain protein, GdpS (for GGDEF domain protein from **Staphylococcus**), and a second protein with a highly modified GGDEF domain, GdpP, are present in the sequenced **staphylococcal** genomes. Here, we investigated the role of GdpS in **biofilm** formation in **Staphylococcus epidermidis** . Inactivation of gdpS impaired **biofilm** formation in medium supplemented with NaCl under static and flow-cell conditions, whereas gdpS overexpression complemented the mutation and enhanced wild-type **biofilm** development. GdpS increased production of the icaADBC-encoded exopolysaccharide, poly-N-acetyl-glucosamine, by elevating icaADBC mRNA levels. Unexpectedly, **c-di-GMP** synthesis was found to be irrelevant for the ability of GdpS to elevate icaADBC expression. Mutagenesis of the GGEEF motif

essential for diguanylate cyclase activity did not impair GdpS, and the N-terminal fragment of GdpS lacking the GGDEF domain partially complemented the gdpS mutation. Furthermore, heterologous diguanylate cyclases expressed in trans failed to complement the gdpS mutation, and the purified GGDEF domain from GdpS possessed no diguanylate cyclase activity in vitro. The gdpS gene from **Staphylococcus** aureus exhibited similar characteristics to its S. **epidermidis** ortholog, suggesting that the GdpS-mediated signal transduction is conserved in **staphylococci**. Therefore, GdpS affects **biofilm** formation through a novel **c-di-GMP** -independent mechanism involving increased icaADBC mRNA levels and exopolysaccharide biosynthesis. Our data raise the possibility that **staphylococci** cannot synthesize **c-di- GMP** and have only remnants of a **c-di- GMP** signaling pathway.

CT Amino Acid Sequence
***Biofilms: GD, growth & development**
***Cyclic GMP: AA, analogs & derivatives**
Cyclic GMP: ME, metabolism
Gene Deletion
Gene Dosage
Gene Expression Profiling
*Gene Expression Regulation
Genetic Complementation Test
Molecular Sequence Data
Mutagenesis, Insertional
Mutagenesis, Site-Directed
Mutation
Phosphorus-Oxygen Lyases: GE, genetics
*Phosphorus-Oxygen Lyases: ME, metabolism
Polysaccharides, Bacterial: BI, biosynthesis
Sequence Alignment
Sequence Deletion
Staphylococcus aureus: EN, enzymology
Staphylococcus aureus: GE, genetics
Staphylococcus epidermidis: EN, enzymology
Staphylococcus epidermidis: GE, genetics
***Staphylococcus epidermidis: PH, physiology**

RN **61093-23-0 (bis(3',5')-cyclic diguanylic acid); 7665-99-8 (Cyclic GMP)**

L59 ANSWER 25 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2007652249 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 17586641
TITLE: BifA, a cyclic-Di-GMP phosphodiesterase, inversely regulates **biofilm** formation and swarming motility by Pseudomonas aeruginosa PA14.
AUTHOR: Kuchma Sherry L; Brothers Kimberly M; Merritt Judith H; Liberati Nicole T; Ausubel Frederick M; O'Toole George A
CORPORATE SOURCE: Department of Microbiology and Immunology, Dartmouth Medical School, Rm. 505, Vail Building, North College St., Hanover, NH 03755, USA.
CONTRACT NUMBER: 1-P20-RR01878 (United States NCRR NIH HHS)
AI51360 (United States NIAID NIH HHS)
SOURCE: Journal of bacteriology, (2007 Nov) Vol. 189, No. 22, pp. 8165-78. Electronic Publication: 2007-06-22.
Journal code: 2985120R. E-ISSN: 1098-5530.
Report No.: NLM-PMC2168662.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200801
ENTRY DATE: Entered STN: 6 Nov 2007
Last Updated on STN: 15 Jan 2008
Entered Medline: 14 Jan 2008

AB The intracellular signaling molecule, cyclic-di-GMP (**c- di-GMP**), has been shown to influence bacterial behaviors, including motility and **biofilm** formation. We report the identification and characterization of PA4367, a gene involved in regulating surface-associated behaviors in Pseudomonas aeruginosa. The PA4367 gene encodes a protein with an EAL domain, associated with **c-di-GMP** phosphodiesterase activity, as well as a GGDEF domain, which is associated with a **c-di- GMP**-synthesizing diguanylate cyclase activity. Deletion of the PA4367 gene results in a severe defect in swarming motility and a hyperbiofilm phenotype; thus, we designate this gene bifA, for **biofilm** formation. We show that BifA localizes to the inner **membrane** and, in biochemical studies, that purified BifA protein exhibits phosphodiesterase activity in vitro but no detectable diguanylate cyclase activity. Furthermore, mutational analyses of the conserved EAL and GGDEF residues of BifA suggest that both domains are important for the observed phosphodiesterase activity. Consistent with these data, the DeltabifA mutant exhibits increased cellular pools of **c- di-GMP** relative to the wild type and increased synthesis of a polysaccharide produced by the pel locus. This increased polysaccharide production is required for the enhanced **biofilm** formed by the DeltabifA mutant but does not contribute to the observed swarming defect. The DeltabifA mutation also results in decreased flagellar reversals. Based on epistasis studies with the previously described sadB gene, we propose that BifA functions upstream of SadB in the **control** of **biofilm** formation and swarming.

TI BifA, a cyclic-Di-GMP phosphodiesterase, inversely regulates **biofilm** formation and swarming motility by Pseudomonas aeruginosa PA14.

AB The intracellular signaling molecule, cyclic-di-GMP (**c- di-GMP**), has been shown to influence bacterial behaviors, including motility and **biofilm** formation. We report the identification and characterization of PA4367, a gene involved in regulating surface-associated behaviors in Pseudomonas aeruginosa. The PA4367 gene encodes a protein with an EAL domain, associated with **c-di-GMP** phosphodiesterase activity, as well as a GGDEF domain, which is associated with a **c-di- GMP**-synthesizing diguanylate cyclase activity. Deletion of the PA4367 gene results in a severe defect in swarming motility and a hyperbiofilm phenotype; thus, we designate this gene bifA, for **biofilm** formation. We show that BifA localizes to the inner **membrane** and, in biochemical studies, that purified BifA protein exhibits phosphodiesterase activity in vitro but no detectable diguanylate cyclase activity. Furthermore, mutational analyses of the conserved EAL and GGDEF residues of BifA suggest that both domains are important for the observed phosphodiesterase activity. Consistent with these data, the DeltabifA mutant exhibits increased cellular pools of **c- di-GMP** relative to the wild type and increased synthesis of a polysaccharide produced by the pel locus. This increased polysaccharide production is required for the enhanced **biofilm** formed by the DeltabifA mutant but does not contribute to the observed swarming defect. The DeltabifA mutation also results in decreased flagellar reversals. Based on epistasis studies with the previously described sadB gene, we propose that BifA functions upstream of SadB in the **control** of **biofilm** formation and swarming.

CT Bacterial Proteins: GE, genetics
Bacterial Proteins: ME, metabolism
***Biofilms: GD, growth & development**
Cell Membrane
***Cyclic GMP: AA, analogs & derivatives**

Cyclic GMP: ME, metabolism
Gene Expression Regulation, Bacterial
Movement
Phosphoric Diester Hydrolases: GE, genetics
*Phosphoric Diester Hydrolases: ME, metabolism
Protein Transport
*Pseudomonas aeruginosa: CY, cytology
*Pseudomonas aeruginosa: EN, enzymology
RN **61093-23-0 (bis(3',5')-cyclic diguanylic acid); 7665-99-8 (Cyclic GMP)**

L59 ANSWER 26 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2006157240 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 16547056
TITLE: Control of formation and cellular detachment from Shewanella oneidensis MR-1 **biofilms** by cyclic di-GMP.
AUTHOR: Thormann Kai M; Duttler Stefanie; Saville Renee M; Hyodo Mamoru; Shukla Soni; Hayakawa Yoshihiro; Spormann Alfred M
CORPORATE SOURCE: Department of Civil Engineering, James H. Clark Center for Biomedical Engineering and Science, Stanford University, Stanford, CA 94305-5429, USA.
SOURCE: Journal of bacteriology, (2006 Apr) Vol. 188, No. 7, pp. 2681-91.
Journal code: 2985120R. ISSN: 0021-9193.
Report No.: NLM-PMC1428383.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200604
ENTRY DATE: Entered STN: 21 Mar 2006
Last Updated on STN: 26 Apr 2006
Entered Medline: 25 Apr 2006

AB Stability and resilience against environmental perturbations are critical properties of medical and environmental **biofilms** and pose important targets for their control. **Biofilm** stability is determined by two mutually exclusive processes: attachment of cells to and detachment from the **biofilm** matrix. Using Shewanella oneidensis MR-1, an environmentally versatile, Fe(III) and Mn(IV) mineral-reducing microorganism, we identified mxdABCD as a new set of genes essential for formation of a three-dimensional **biofilm**. Molecular analysis revealed that mxdA encodes a cyclic bis(3',5')guanylic acid (cyclic di-GMP)-forming enzyme with an unusual GGDEF motif, i.e., NVDEF, which is essential for its function. mxdB encodes a putative **membrane** -associated glycosyl transferase. Both genes are essential for matrix attachment. The attachment-deficient phenotype of a DeltamxdA mutant was rescued by ectopic expression of VCA0956, encoding another diguanylate cyclase. Interestingly, a rapid cellular detachment from the **biofilm** occurred upon induction of yhjH, a gene encoding an enzyme that has been shown to have phosphodiesterase activity. In this way, it was possible to bypass the previously identified sudden depletion of molecular oxygen as an environmental trigger to induce **biofilm** dissolution. We propose a model for **c-di-GMP** as a key intracellular regulator for **controlling biofilm** stability by shifting the state of a **biofilm** cell between attachment and detachment in a concentration-dependent manner.
TI Control of formation and cellular detachment from Shewanella oneidensis MR-1 **biofilms** by cyclic di-GMP.
AB Stability and resilience against environmental perturbations are critical properties of medical and environmental **biofilms** and pose important targets for their control. **Biofilm** stability is determined by two mutually exclusive

processes: attachment of cells to and detachment from the **biofilm** matrix. Using Shewanella oneidensis MR-1, an environmentally versatile, Fe(III) and Mn(IV) mineral-reducing microorganism, we identified mxdABCD as a new set of genes essential for formation of a three-dimensional **biofilm**. Molecular analysis revealed that mxdA encodes a cyclic bis(3',5')guanylic acid (cyclic di-GMP)-forming enzyme with an unusual GGDEF motif, i.e., NVDEF, which is essential for its function. mxdB encodes a putative **membrane** -associated glycosyl transferase. Both genes are essential for matrix attachment. The attachment-deficient phenotype of a DeltamxdA mutant was rescued by ectopic expression of VCA0956, encoding another diguanylate cyclase. Interestingly, a rapid cellular detachment from the **biofilm** occurred upon induction of yhjH, a gene encoding an enzyme that has been shown to have phosphodiesterase activity. In this way, it was possible to bypass the previously identified sudden depletion of molecular oxygen as an environmental trigger to induce **biofilm** dissolution. We propose a model for **c-di-GMP** as a key intracellular regulator for **controlling biofilm** stability by shifting the state of a **biofilm** cell between attachment and detachment in a concentration-dependent manner.

CT Bacterial Adhesion
***Biofilms: GD, growth & development**
***Cyclic GMP: AA, analogs & derivatives**
Cyclic GMP: ME, metabolism
Gene Expression Regulation, Bacterial
Operon
Polysaccharides: ME, metabolism
Shewanella: GE, genetics
*Shewanella: PH, physiology
Shewanella: UL, ultrastructure

RN **61093-23-0 (bis(3',5')-cyclic diguanylic acid); 7665-99-8 (Cyclic GMP)**

L59 ANSWER 27 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2005389798 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 16048911
TITLE: **3',5'-cyclic diguanylic acid reduces** the virulence of **biofilm**-forming **Staphylococcus** aureus strains in a mouse model of mastitis infection.
AUTHOR: Brouillette Eric; Hyodo Mamoru; Hayakawa Yoshihiro; Karaolis David K R; Malouin Francois
CORPORATE SOURCE: CEVDM, Departement de biologie, Faculte des sciences, Universite de Sherbrooke, 2500 Boul. Universite, Sherbrooke, Quebec, Canada.
SOURCE: Antimicrobial agents and chemotherapy, (2005 Aug) Vol. 49, No. 8, pp. 3109-13.
Journal code: 0315061. ISSN: 0066-4804.
Report No.: NLM-PMC1196217.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200509
ENTRY DATE: Entered STN: 29 Jul 2005
Last Updated on STN: 20 Sep 2005
Entered Medline: 19 Sep 2005

AB The cyclic dinucleotide **3',5'-cyclic diguanylic acid (c-di-GMP)** is a naturally occurring small molecule that regulates important signaling systems in bacteria. We have recently shown that **c-di -GMP inhibits Staphylococcus** aureus **biofilm** formation in vitro and its adherence to HeLa cells. We now

report that **c-di-GMP treatment** has an antimicrobial and antipathogenic activity in vivo and **reduces**, in a dose-dependent manner, **bacterial** colonization by **biofilm**-forming S. aureus strains in a mouse model of mastitis infection. Intramammary injections of 5 and 50 nmol of **c-di-GMP decreased colonization** (**bacterial** CFU per gram of gland) by 0.79 ($P > 0.05$) and 1.44 ($P < 0.01$) logs, respectively, whereas 200-nmol doses allowed clearance of the bacteria below the detection limit with a reduction of more than 4 logs ($P < 0.001$) compared to the untreated control groups. These results indicate that cyclic dinucleotides potentially represent an attractive and novel drug platform which could be used alone or in combination with other agents or drugs in the **prevention, treatment**, or **control** of **infection.**

TI **3',5'-cyclic diguanylic acid reduces** the virulence of **biofilm**-forming **Staphylococcus** aureus strains in a mouse model of mastitis infection.

AB The cyclic dinucleotide **3',5'-cyclic diguanylic acid (c-di-GMP)** is a naturally occurring small molecule that regulates important signaling systems in bacteria. We have recently shown that **c-di -GMP inhibits Staphylococcus** aureus **biofilm** formation in vitro and its adherence to HeLa cells. We now report that **c-di-GMP treatment** has an antimicrobial and antipathogenic activity in vivo and **reduces**, in a dose-dependent manner, **bacterial** colonization by **biofilm**-forming S. aureus strains in a mouse model of mastitis infection. Intramammary injections of 5 and 50 nmol of **c-di-GMP decreased colonization** (**bacterial** CFU per gram of gland) by 0.79 ($P > 0.05$) and 1.44 ($P < 0.01$) logs, respectively, whereas 200-nmol doses allowed clearance of the bacteria below the detection limit with a reduction of more than 4 logs ($P < 0.001$) compared to the untreated control groups. These results indicate that cyclic dinucleotides potentially represent an attractive and novel drug platform which could be used alone or in combination with other agents or drugs in the **prevention, treatment**, or **control** of **infection.**

CT Check Tags: Female
Animals
Anti-Bacterial Agents: PD, pharmacology
*Anti-Bacterial Agents: TU, therapeutic use
***Biofilms: DE, drug effects**
Biofilms: GD, growth & development
Cattle
***Cyclic GMP: AA, analogs & derivatives**
Cyclic GMP: PD, pharmacology
Cyclic GMP: TU, therapeutic use
*Mastitis, Bovine: DT, drug therapy
Mastitis, Bovine: MI, microbiology
Mastitis, Bovine: PP, physiopathology
Mice
Models, Animal
Staphylococcal Infections: DT, drug therapy
Staphylococcal Infections: MI, microbiology
Staphylococcal Infections: PP, physiopathology
***Staphylococcus aureus: DE, drug effects**
Staphylococcus aureus: GD, growth & development
***Staphylococcus aureus: PY, pathogenicity**
Virulence

RN **61093-23-0 (bis(3',5')-cyclic diguanylic acid); 7665-99-8 (Cyclic GMP)**

L59 ANSWER 28 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2002001765 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11751251
TITLE: NO/**cGMP** signaling and HSP90 activity represses metamorphosis in the sea urchin Lytechinus pictus.

AUTHOR: Bishop C D; Brandhorst B P
CORPORATE SOURCE: Department of Molecular Biology and Biochemistry, Simon Fraser University, Burnaby, British Columbia V5A 1S6, Canada.
SOURCE: The Biological bulletin, (2001 Dec) Vol. 201, No. 3, pp. 394-404.
Journal code: 2984727R. ISSN: 0006-3185.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 2 Jan 2002
Last Updated on STN: 3 Apr 2002
Entered Medline: 28 Mar 2002

AB Nitric oxide (NO) signaling repressively regulates metamorphosis in two solitary ascidians and a gastropod. We present evidence for a similar role in the sea urchin Lytechinus pictus. NO commonly signals via soluble guanylyl cyclase (sGC). Nitric oxide synthase (NOS) activity in some **mammalian** cells, including neurons, depends on the molecular chaperone heat shock protein 90 (HSP90); this may be so in echinoid larvae as well. Pluteus larvae containing juvenile rudiments were **treated** with either radicicol L- or D-nitroarginine-methyl-ester (L-NAME and D-NAME), or IH-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one (ODQ), inhibitors of HSP90, NOS, and sGC, respectively. In all instances, drug **treatment** significantly increased the frequency of metamorphosis. SNAP, a NO donor, suppressed the inductive properties of L-NAME and **biofilm**, a natural inducer of metamorphosis. NADPH diaphorase histochemistry indicated NOS activity in cells in the lower lip of the larval mouth, the preoral hood, the gut, and in the tube feet of the echinus rudiment. Histochemical staining coincided with NOS immunostaining. Microsurgical removal of the oral hood or the pre-oral hood did not induce metamorphosis, but larvae lacking these structures retained the capacity to metamorphose in response to ODQ. We propose that the production of NO repressively regulates the initiation of metamorphosis and that a sensory response to environmental cues reduces the production of NO, and consequently **cGMP**, to initiate metamorphosis.

TI NO/**cGMP** signaling and HSP90 activity represses metamorphosis in the sea urchin Lytechinus pictus.

AB Nitric oxide (NO) signaling repressively regulates metamorphosis in two solitary ascidians and a gastropod. We present evidence for a similar role in the sea urchin Lytechinus pictus. NO commonly signals via soluble guanylyl cyclase (sGC). Nitric oxide synthase (NOS) activity in some **mammalian** cells, including neurons, depends on the molecular chaperone heat shock protein 90 (HSP90); this may be so in echinoid larvae as well. Pluteus larvae containing juvenile rudiments were **treated** with either radicicol L- or D-nitroarginine-methyl-ester (L-NAME and D-NAME), or IH-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one (ODQ), inhibitors of HSP90, NOS, and sGC, respectively. In all instances, drug **treatment** significantly increased the frequency of metamorphosis. SNAP, a NO donor, suppressed the inductive properties of L-NAME and **biofilm**, a natural inducer of metamorphosis. NADPH diaphorase histochemistry indicated NOS activity in cells in the lower lip of the larval mouth, the preoral hood, the gut, and in the tube feet of the echinus rudiment. Histochemical staining coincided with NOS immunostaining. Microsurgical removal of the oral hood or the pre-oral hood did not induce metamorphosis, but larvae lacking these structures retained the capacity to metamorphose in response to ODQ. We propose that the production of NO repressively regulates the initiation of metamorphosis and that a sensory response to environmental cues reduces the production of NO, and consequently **cGMP**, to initiate metamorphosis.

CT Check Tags: Female; Male
Animals

***Cyclic GMP: PH, physiology**
*Enzyme Inhibitors: PD, pharmacology
Guanylate Cyclase: AI, antagonists & inhibitors
*HSP90 Heat-Shock Proteins: PH, physiology
Lactones: PD, pharmacology
Macrolides
Metamorphosis, Biological: DE, drug effects
*Metamorphosis, Biological: PH, physiology
NG-Nitroarginine Methyl Ester: PD, pharmacology
*Nitric Oxide: PH, physiology
Nitric Oxide Donors: PD, pharmacology
Nitric Oxide Synthase: AI, antagonists & inhibitors
Oxadiazoles: PD, pharmacology
Quinoxalines: PD, pharmacology
S-Nitroso-N-Acetylpenicillamine: PD, pharmacology
Sea Urchins: DE, drug effects
*Sea Urchins: GD, growth & development
Sea Urchins: PH, physiology
Signal Transduction: DE, drug effects
*Signal Transduction: PH, physiology
RN 10102-43-9 (Nitric Oxide); 12772-57-5 (monorden); 50903-99-6 (NG-Nitroarginine Methyl Ester); **7665-99-8 (Cyclic GMP)**; 79032-48-7 (S-Nitroso-N-Acetylpenicillamine)

L59 ANSWER 29 OF 30 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2009247317 EMBASE Full-text
TITLE: In vivo evaluation of vaginal films for **mucosal** delivery of nitric oxide.
AUTHOR: Yoo, Jin-Wook; Acharya, Gayathri; Lee, Chi H. (correspondence)
CORPORATE SOURCE: Division of Pharmaceutical Sciences, School of Pharmacy, University of Missouri at Kansas City, 5005 Rockhill Rd, MO 64110, United States. leech@umkc.edu
SOURCE: Biomaterials, (August 2009) Vol. 30, No. 23-24, pp. 3978-3985.
Refs: 38
ISSN: 0142-9612 CODEN: BIMADU
PUBLISHER: Elsevier Ltd, Langford Lane, Kidlington, Oxford, OX5 1GB, United Kingdom.
PUBLISHER IDENT.: S 0142-9612(09)00350-0
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 16 Jun 2009
Last Updated on STN: 16 Jun 2009

AB Nitric oxide (NO)-releasing vaginal films were developed and evaluated as a potential advanced treatment option for female sexual arousal disorder (FSAD). The polymeric films containing s-nitrosoglutathione (GSNO), an endogenous NO donor, were prepared using the reduced-pressure drying method. The surface morphology, thermal/mechanical properties, stability, loading efficiency and physicodynamic properties were characterized and the pharmacological activities were evaluated through in vitro and in vivo studies. The GSNO films were homogeneous and transparent, and showed suitable mucoadhesiveness and mechanical properties. The release profiles of NO from the GSNO films followed the first-order kinetic pattern and NO activated the NO-**cGMP** signaling pathway in vaginal cells. The GSNO films significantly enhanced the

duration of action of GSNO and vagina blood perfusion in the rat model without causing any cytotoxic effects. The NO-releasing vaginal films might be used as a promising treatment device against FSAD.

TI In vivo evaluation of vaginal films for **mucosal** delivery of nitric oxide.

AB Nitric oxide (NO)-releasing vaginal films were developed and evaluated as a potential advanced treatment option for female sexual arousal disorder (FSAD). The polymeric films containing s-nitrosoglutathione (GSNO), an endogenous NO donor, were prepared using the reduced-pressure drying method. The surface morphology, thermal/mechanical properties, stability, loading efficiency and physicodynamic properties were characterized and the pharmacological activities were evaluated through in vitro and in vivo studies. The GSNO films were homogeneous and transparent, and showed suitable mucoadhesiveness and mechanical properties. The release profiles of NO from the GSNO films followed the first-order kinetic pattern and NO activated the NO-**cGMP** signaling pathway in vaginal cells. The GSNO films significantly enhanced the duration of action of GSNO and vagina blood perfusion in the rat model without causing any cytotoxic effects. The NO-releasing vaginal films might be used as a promising treatment device against FSAD.

CT Medical Descriptors:
animal experiment
article
***biofilm**
cell type
controlled study
cytotoxicity
*drug delivery system
drug release
drug stability
female
female sexual dysfunction
human
human cell
in vitro study
in vivo study
morphology
mucoadhesion
nonhuman
perfusion
priority journal
rat
sexual arousal disorder
vagina cell
*vaginal film

CT Drug Descriptors:
carbomer: PR, pharmaceutics
cyclic GMP: EC, endogenous compound
hydroxypropylmethylcellulose: PR, pharmaceutics
macrogol: PR, pharmaceutics
methylcellulose
*nitric oxide: PR, pharmaceutics
s nitrosoglutathione: PR, pharmaceutics
s nitrosoglutathione: TP, topical drug administration

RN (carbomer) 9007-20-9, 9062-04-8; (**cyclic GMP**) **7665-99-8**; (hydroxypropylmethylcellulose) 9004-65-3; (macrogol) 25322-68-3; (methylcellulose) 79484-92-7, 9004-67-5; (nitric oxide) 10102-43-9; (s nitrosoglutathione) 57564-91-7

L59 ANSWER 30 OF 30 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2009280434 EMBASE Full-text
TITLE: Signals, regulatory networks, and materials that build and break bacterial **biofilms.**
AUTHOR: Karatan, Ece (correspondence)
CORPORATE SOURCE: Department of Biology, Appalachian State University, Boone, NC 28608, United States. karatane@appstate.edu
AUTHOR: Watnick, Paula
CORPORATE SOURCE: Division of Infectious Diseases, Children's Hospital, Boston, MA 02115, United States.
AUTHOR: Watnick, Paula
CORPORATE SOURCE: Department of Microbiology and Molecular Genetics, Harvard Medical School, Boston, MA 02115, United States.
SOURCE: Microbiology and Molecular Biology Reviews, (June 2009) Vol. 73, No. 2, pp. 310-347.
Refs: 363
ISSN: 1092-2172 CODEN: MMBRF7
PUBLISHER: American Society for Microbiology, 1752 N Street N.W., Washington, DC 20036-2904, United States.
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 004 Microbiology: Bacteriology, Mycology, Parasitology and Virology
LANGUAGE: English
ENTRY DATE: Entered STN: 7 Jul 2009
Last Updated on STN: 7 Jul 2009

TI Signals, regulatory networks, and materials that build and break bacterial **biofilms.**

CT Medical Descriptors:
antibiotic resistance
bacterial flagellum
***bacterial membrane**
bacterium pilus
***biofilm**
Caulobacter crescentus
materials testing
molecular biology
nonhuman
Pseudomonas aeruginosa
Pseudomonas fluorescens
regulatory mechanism
review
Salmonella typhimurium
second messenger
signal transduction
transcription regulation
Vibrio cholerae
Vibrio harveyi
Yersinia enterocolitica
Yersinia pseudotuberculosis

CT Drug Descriptors:
*adhesin: EC, endogenous compound
antiinfective agent
cyclic AMP: EC, endogenous compound
cyclic GMP: EC, endogenous compound
exopolysaccharide
glucose
iron
monosaccharide
tobramycin

RN (cyclic AMP) 60-92-4; **(cyclic GMP) 7665-99-8**